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DEPRESSIVE STATES: THEIR AETIOLOGY AND TREATMENT*

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Depression is a large subject, and the purpose of this paper is to discuss merely a few aspects of it. Some years ago a front page to the out-patient notes of psychiatric patients attending Westminster Hospital was devised which was intended to give the essential facts of the case when the patient came up on subsequent occasions. It was envisaged, of course, that the data collected might be examined, for the hospital is fortunate in having a records officer and a Powers-Samas machine; but no particular piece of research was in mind at the time. These points are mentioned since it is relevant to notice that the original observations were made without any motive save of a very general kind, and the results, being computed by a machine, should be free from the unconscious distortion that can sometimes mar such retrospective studies. Data of this kind could be produced for any psychiatric syndrome, and a study of anxiety states on somewhat similar lines has already been published (Garmany, 1956).

A group of 525 consecutive cases has been chosen, comprising depressive states of all kinds. In each of these an effect of sadness would be both dominant and primary, and the series should not include, for example, anxiety states with depressive features or schizophrenia presenting with depression. At the time each patient was seen the depressive was classified as endogenous, reactive, or involutional, and this classification is preserved in the data which follow. In considering, as we must, how the distinction was made, it may be noted that the vast majority of the assessments were made by me. It is not suggested that this fact confers upon them any quality save a relative uniformity of approach.

Classification of Depression

Endogenous depression, as its name suggests, is a depression coming from within, which means much the same as idiopathic and essential in other contexts—namely, that we do not know why it happens at all. Coming without apparent cause, it usually runs a self-limited course of six to nine months, and this period can be greatly shortened in the large majority of cases by electroplexy. The family history is often positive, and there is some correlation between the tendency to develop this form of depression and the possession of a pyknic habitus, of which the familiar picture of John Bull is a typical example. The well-known work of Kretschmer in this context has not been an unmixed blessing to psychiatrists, many of whom have a strong resistance to the recognition of endogenous depression in those of asthenic habitus. Sometimes these patients are suspected quite unjustly of concealing important psychopathological data, or, alternatively, much time may be spent in working on material which is present but irrelevant.

In making a diagnosis of endogenous depression I have been influenced by many factors. An absence of precipitating causes is clearly one, for it is implicit in the definition of the disease. A history of periodic attacks with recovery in between, either in the patient or in members of his family, is important. Equally so is the presence of a temperament known to predispose to the disease, whether it be depressive, hypomanic, or cycloid—moving between the two extremes. Finally, I have been influenced by the cross-sectional picture which has been regarded as typical of endogenous depression. Such a picture would include remorse and self-blame about the past, hopelessness about the prospects of future recovery, and psychomotor retardation. In very few cases would all these things be present, but enough would usually be there for a confident diagnosis to be made. To what extent such confidence was justified is one of the questions to be considered.

Reactive depression is regarded as a progressive reaction to events, in the Meyerian sense, and not as a disease entity, as is endogenous depression. It is therefore in theory traumatic, and, as was noted during the war, trauma is more effective in producing the illness when it is slight but sustained than when it is acute but short-lived. The diagnosis is therefore made when a depressive illness follows upon sustained trauma, and it is particularly liable to follow a long period of tension (Curran and Garmany, 1944). The cross-sectional picture is traditionally a different one from that presented by an endogenous depression.

Psychomotor retardation is not present, and blame of others for his plight is more usual than remorse. Hopelessness about recovery is uncommon, and so, for the same reason, is suicidal preoccupation. The diagnosis is sometimes influenced by the probable or known results of treating the patient with electroplexy, on the basis that if the patient responds his illness could not have been psychogenic, a conclusion which is neither logical nor true.

In making a diagnosis of *involutional depression* I have used far stricter criteria of a classical kind. To fall within this group the patient had to be of an age ranging from one corresponding with that of the menopause in women and extending up to old age. The

*A shortened version of an address to the Folkestone Medical Society on April 24, 1958.

pre-morbid personality had to be of a rigid and rather obsessional kind, quite dissimilar from the likable pyknic of tradition. There should have been no previous attacks, and the clinical picture should show both agitation and hypochondriasis. I think it is true to say that these five criteria have been accepted in psychiatry for a long time, though in clinical practice they are seldom followed strictly. I have followed them myself, however, largely in order that I should know in the future what I meant when I saw the patient. The comparatively small number of involutional depressions in the series is probably to be attributed to this rather purist approach, and illustrates very well the difficulties in making comparisons in psychiatry when the criteria of diagnosis can vary so much.

Distribution between Endogenous and Reactive Depression

There has for many years been dissension among psychiatrists regarding the reality of the distinction between endogenous depression and reactive depression, and regarding the existence of involutional depression as an entity at all. Lewis (1934) in a paper which is now securely ensconced among the classics of psychiatry, attempted to answer the first of these problems. In a very careful study he was unable to satisfy himself that there was any real difference between reactive and endogenous depression, at least in terms of symptoms. Mayer-Gross *et al.* (1954), on the other hand, take the opposite view, and feel that, though the distinction may be difficult to make in many cases, it can and should be made. The problem is one of exceptional difficulty because of the universal human tendency to seek causes for the effects it witnesses. Thus it happens that both the patient with the endogenous depression and his relatives may produce all kinds of apparent aetiological factors, many of which are really the results or content of the illness rather than its cause.

Life is full of troubles, and it is statistically not unlikely that, whenever an endogenous depression begins, some traumatic incident will have preceded it, so that the one is regarded as the result of the other. The psychiatrist himself may be in a dilemma too, for if, as is usual, he regards a certain clinical syndrome as being typical of a constitutional illness—namely, endogenous depression—he may disregard dynamic external factors which are important. Thus I feel no doubt at all that influenza frequently precipitates a depression which is clinically of an endogenous type, and yet that fact should not be so if our description is correct.

A similar problem arises in the case of reactive depression. Traumatic events may precede the illness and yet we may be dealing with a temporal coincidence. A notable example is the prolonged grief reaction following death in the family circle. Depressive manifestations occur physiologically for about three months, and yet the same picture may be evident perhaps five years after the death. While on the face of it such a depressive is reactive, it is noteworthy that a considerable proportion will respond to electroplexy.

The distinction, if any, between endogenous and reactive depression is often posed as a problem which seems only verbal. Nevertheless there are certain very real questions to be answered. Firstly, we ought to know whether depressions generally can be divided into those in which constitutional factors are all-important and environmental factors of little account, and others in which the reverse applies. Secondly, and supposing the first question is answered affirmatively, we must know whether it is true that endogenous depression should be treated by E.C.T. and reactive depression by psychotherapy; for that is the usual assumption. Everyone would agree that a few cases fall clearly into one group or the other, but we must know whether the distinction is a valid one for the group as a whole. The results which are here reported bear principally upon these two questions of aetiology and treatment.

In some respects, and particularly when considering treatment, the results reported have certain limitations. They are derived from the out-patient population of a London teaching hospital and cannot be representative of the population as a whole. Many general-practitioner colleagues recognize and treat depressions on conservative lines without referring them for an opinion. Many potential patients do not become actually so because they cope with their own affective disturbances. For these reasons the patients seen probably exclude many minor cases, but, as will be apparent, this lends greater point to some of the inferences made. In London the urgent disposal of acutely suicidal patients is facilitated by the highly organized public health service, so that with such patients the doctor may often send for a duly authorized officer himself. I am inclined to think that the deviation of patients in this way is probably small in the case of depression, while it might be quite considerable in the case, say, of acute schizophrenic episodes.

Aetiology

Table I shows the incidence of constitutional loading in 525 consecutive cases of depression seen at Westminster Hospital. The cases are broken down into their three categories, and for interest the corresponding percentages are shown for anxiety states and taken from the paper to which reference has been made. Constitution means the general mental and physical make-up of the patient, and "loading" has been inferred from a number of factors. Thus a pyknic habitus, a positive family history, and a history in the patient of previous unprovoked attacks were taken as indications of constitutional predisposition. The word "notable" means that such indications have been marked and unmistakable. The word "possible" has not in fact been used in the sense I originally intended—namely, to indicate a state of doubt. In practice it has meant "likely," and so in assessing the results I have added these two columns together. It will be seen that, although the loading is greater in the endogenous cases, it is nevertheless very high in all three categories. Bearing in mind that the presence of such loading has to some extent influenced me in diagnosing endogenous depression at all, I do not feel that the difference between 70% and 55% is enough to warrant much support for a clear differentiation between the two types of depression.

TABLE I.—*Incidence of Constitutional Loading in 525 Cases of Depression*

	Endogenous Depression	Reactive Depression	Involutional Depression	Anxiety States
No. of Cases	295	194	36	
Notable	98 } 70%	40 } 55%	5 } 47%	61%
Possible	107 }	67 }	12 }	
Unlikely	85	70	13	38%
Not stated ..	5	17	6	3

Table II shows a list of stress factors enumerated at the time the cases were first seen. They were present at the time the illness developed and were considered to be aetiologically important in its development and perpetuation. Thus if after influenza a depression developed with a typical "endogenous" appearance, I would mark the illness as being associated with a physical stress factor, since to do

TABLE II.—*Stress Factors*

	Endogenous Depression	Reactive Depression	Involutional Depression	Anxiety States
No. of Cases:	295	194	36	
Personal	170 (58%)	115 (59%)	24 (66·6%)	70%
Domestic	83 (29%)	94 (48%)	3 (8·3%)	35%
Work	38 (13%)	35 (18%)	8 (22%)	20%
Other social ..	15 (5%)	17 (9%)	0	10%
Financial	13 (4·3%)	20 (10%)	1 (3%)	9%
Housing	11 (3·6%)	8 (4%)	0	9%
Physical	51 (17%)	80 (41%)	3 (8·3%)	27%
None found ..	64 (21%)	11 (5·1%)	8 (22%)	9%

otherwise seems against reason and good sense. Similarly, if a man developed an endogenous depression with motor retardation and told me that the illness arose after his wife had left him, then I would mark this as a domestic stress factor rather than dismiss it as mere content of his illness. The personal stress factor requires some explanation, since it has been used in a special sense, and it must be distinguished from constitution.

Constitution refers in this context to an inborn loading which predisposes to depression. Personal stress factors mean those facets of personality structure which make living less easy, but do *not* of themselves predispose to depression. Thus an overactive conscience may be acquired in a strictly religious family, and would make life in a stockbroker's office more of an exercise than it would be in a vicarage. This would be recorded as a personal stress factor. The meticulous obsessional character creates what to others may seem to be unnecessary burdens for itself. It delegates badly, it concerns itself overmuch with trivia, and it sets out to live up to standards of performance which are abnormally high. This is not depressive loading, but it certainly constitutes a stress factor of some magnitude. These then are the senses in which I have used these two expressions, and it is because others might use them differently that I feel I should describe them.

It will be noted in Table II that the percentages add up to more than 100 because, of course, several factors might be operative in one particular patient. There is no doubt that the incidence of stress factors, other than personal ones, is higher in the reactive group than in the endogenous group. Nevertheless it is high in both columns, and the intrapersonality stresses were the same in both. I was extremely surprised to find that domestic stresses had been thought to be important in almost one-third of the cases of endogenous depression seen and in nearly half of the cases of reactive depression. Had I been given these figures before they were computed I would have thought them exaggerated. This is perhaps an interesting example of how superior old traditions can be when contrasted with the newer psychiatry. Most women regard development of depression in a husband as a serious personal reflection, and it would appear that in a large proportion of cases they are right. Because of a rather unhappy oversight when the transcriptions were drawn up, the machine has proved incapable of sex differentiation, and I cannot therefore give figures which would inculpate husbands.

The important role of physical factors in reactive depression is noteworthy, though this must, in some measure at least, be the result of work done in a general hospital, since nearly half the patients seen come from colleagues who may have been dealing with associated physical anomalies. Financial difficulties and the housing shortage, as in the case of anxiety states, appear to play little part in aetiology. It is interesting to note that in only 20% of cases did endogenous depression seem to come "out of the blue"—that is to say, without external factors, and, interestingly enough, this is almost exactly what Rennie (1942) found. It may, of course, be said that I have mistaken content for cause, for this criticism was made of Rennie's figures. I cannot prove that this is not so, but can only emphasize that I counted these stress factors only in those instances where temporal coincidence suggested that I must. To have done otherwise would have been to assume the truth of a proposition that I hoped to investigate.

Although diagnosis was made largely on the cross-sectional picture, it is likely that it was influenced in some measure by the presence or absence of stress factors. Thus here, as with constitutional loading, the assessments are in some degree biased. There is no way of measuring this bias, but, making allowance for it as fairly as I can, there does not seem to be any gross dissimilarity among the three groups.

Table III shows the age distribution of the three groups compared with that of anxiety states. The figures are much the same as those given by others. It will be seen that the risk from depression extends over a much longer period of life than does that from tension, which is at its peak in the fourth decade.

TABLE III.—*Age Distribution on 10-Year Groups*

	0–21	21–30	31–40	41–50	51–60	61–70	71–
Endogenous depression	—	51	73	76	57	35	3
Reactive depression ..	5	52	42	38	32	21	4
Involutional depression	—	—	—	8	17	9	2
Anxiety states	8	36	66	28	15	4	1

Treatment

The treatment set out in Table IV represents what was decided at the first interview. Subsequent experience of the patient may in some instances have required modification of the course first chosen. Thus a patient selected for psychotherapy may have deteriorated later and required E.C.T. I venture to hope that usually the course chosen will have been proved by events to have been correct, but with the figures available to me I cannot prove that this is so. Even if others, as is possible, have less confidence in this than I have myself, then at least clear information is given about the advice tendered at the first interview. It will be noticed that the totals at the foot of each column do not quite correspond with the total number of cases seen, which is shown in brackets. The intention was that only the major treatment should be indicated, but in some instances I forgot this and ticked two.

TABLE IV.—*Treatment*

	Endogenous Depression	Reactive Depression	Involutional Depression	Anxiety States
Consultation ..	15	28	3	
Counsel	10 (22%)	18 (53%)	1 (28%)	50%
Support	42	55	6	
Intensive	7 (2·3%)	17 (9%)	1	11%
Group	6 (2%)	2 (1%)	0	3%
Relaxation ..	12 (4%)	14 (7%)	3	33%
Environmental adjustment ..	1	5	1	2%
Mental hospital urgently	16 (5·3%)	4 (2%)	3 (9%)	—
Hospital otherwise	47 (15·6%)	20 (10·5%)	3 (9%)	3 cases
E.C.T.	109 (36·3%)	9 (4·5%)	14 (39%)	—
Drugs	57 (19%)	59 (29·5%)	9 (25%)	33%
Other	—	2	1	4 cases
Total ..	322 (295)	233 (194)	45 (36)	

It is interesting to note that electroplexy was selected for immediate use in out-patients in only just over one-third of the cases of endogenous depression. If all cases of depression are taken together, then about 25% were given this treatment. If it is assumed that all cases severe enough to be sent to hospital were given E.C.T., then I believe that about 50% of all cases of depression referred to our out-patient department received this treatment. I am sure this is a clinical finding without bias, for I have no conscious revulsion against E.C.T. comparable, for example, with my dislike of leucotomy. It will be seen that E.C.T. was employed relatively rarely in those cases called reactive depression. The disparity is so great that I think it can be explained in only one way—namely, that the diagnosis was materially affected by the clinical judgment of probable response to E.C.T.

It is important to be clear what this means. It proves nothing about the constitutional loading present or about the incidence of stress factors. It merely indicates that there is a group of depressions rarely requiring E.C.T., and another group (described here as endogenous and involutional) where E.C.T. is required in something between one-third and one-half of the cases. If there is a fundamental distinction between the groups it is to be found in the quality which is considered in the difficult or borderline case. This quality is, I am sure, *reactivity* or the readiness with which the patient will respond emphatically to changes of mood in the examiner. This quality is used to determine the need for E.C.T., the risk of suicide, and, as has been indicated, the diagnosis. Yet if we describe some depressions

as showing less reactivity than others, we mean much the same as when we say the depression is deeper. This is quite different from saying that the depression is more endogenous.

Only a very small number of patients (4.5%) were sent to mental hospitals urgently because of acute depression. A larger number (about 13.5%) were admitted, mainly to Westminster Hospital, for a variety of reasons. Elderly patients and those with certain associated physical diseases would be admitted, particularly if they had long distances to travel or lived alone. Patients showing severe associated tension or depersonalization are much better treated as in-patients, so that E.C.T. may be given under a heavy blanket of sedative. Those who have lost much weight will not usually do well with out-patient E.C.T. and should be admitted so that modified insulin can be given as well. Nevertheless a patient referred to hospital with depression can be assured, as these figures show, that he has four chances in five of being treated as an out-patient.

The figures given for treatment by drugs are misleading in that, rather arbitrarily, they were regarded as subsidiary forms of treatment when associated with E.C.T. or with psychotherapy. As a result they would often be omitted from the transcription sheet. The incidence of associated pharmacological therapy must in fact have been very high.

Summary

A study has been made of 525 patients suffering from depression divided into the three traditional categories of reactive, endogenous, and involutional depression.

The constitutional loading in patients developing these illnesses is in all cases high, but the incidence does not suggest any qualitative difference among the three types.

Stress factors are important in all groups, and stresses produced by abnormal personalities are especially so. Again, a study of these stress factors does not suggest a distinction worth making among the three groups.

Domestic stresses appear to be highly important in the genesis of reactive depression, of considerable importance in endogenous depression, and of small importance in involutional depression.

Endogenous depression, despite its name, appears to come "out of the blue" in only 20% of cases.

Of all cases of depression referred to hospital, 25% need E.C.T. straight away, and a further 25% after admission to hospital.

Very few cases of reactive depression received E.C.T., and it is believed that these patients were characterized above all by their "reactivity" to outside stimuli.

It is concluded that the distinction between these three forms of depression, and particularly between the reactive and endogenous varieties, is an unreal one. Constitutional predisposition and the incidence of stress factors appears to be much the same in these groups.

The distinction traditionally made appears to be a distinction between those depressions which show more reactivity, are less severe, and infrequently require E.C.T. and those depressions showing the reverse features.

It is believed that this resolves itself into a distinction between mild and severe depression.

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PROGNOSIS OF TROPICAL SPRUE

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There has long been doubt regarding the prognosis of tropical sprue, some regarding it as a seriously chronic disorder in which those affected suffer severe and protracted disablement, remain continually susceptible to relapses, and seldom recover completely (Low, 1928). Stitt (1945) gives a typical opinion in stating of sprue: "Unless adequately treated, however, severe cases are ultimately fatal within a period varying from about one to fifteen years." A further relatively unfavourable prognosis is expressed in a recent textbook (Mackie *et al.*, 1954), where of sprue it is written that "more commonly fats in the diet must be restricted permanently and parenteral injections of liver continued at intervals of one to two weeks." Others (Rodriguez-Molina, 1943; Woodruff, 1949) have produced evidence that the disease has a more favourable prognosis.

The reason for this apparent divergence of views may well be that in different studies different types of cases have been followed, that those with a poor prognosis have been patients affected with idiopathic steatorrhoea or non-tropical sprue, and that those with a satisfactory prognosis have been suffering from tropical sprue. The question might, it was thought, be resolved by ascertaining the ultimate outcome of the disease in patients affected with tropical sprue during the last war. If these patients are still suffering from symptoms of sprue, then the tropical variety of this disease must indeed be one with a protracted course and may well have much in common with idiopathic steatorrhoea, which is generally held to be a chronic disorder. If, on the other hand, tropical sprue is followed by only a short period of disability, then a point of difference of considerable diagnostic and aetiological importance would be established. The point is also of importance in the management and disposal of patients suffering from the disease and concerning the advice to be given them regarding diet and consumption of fats.

A Previous Study

Woodruff (1949) carried out a study in which patients invalided from India to Britain with tropical sprue were followed for $2\frac{1}{4}$ to 3 years. Ten years have elapsed since that study was carried out, and it is therefore possible to review the prognosis of some of those patients, using a longer time scale than was possible in 1949.

The patients were originally diagnosed, treated, and invalided from a mobile R.A.F. field hospital in the Arakan; they have now become widely dispersed throughout Britain, the United States, and a number of Commonwealth countries, and therefore it has not been possible to examine them personally. A detailed questionary has accordingly been sent to them, and this report is based upon the answers given in it. Of the 47 patients reported in 1949 (Woodruff, 1949) it had been possible to follow up 34 at that time. Further letters were recently written to these patients and 17 replies were received.

Original Condition of the Patients

The clinical features of the 47 patients with sprue have previously been described (Woodruff, 1949). The records of the 17 patients who replied to the recently issued

questionary have been reviewed and their original symptoms have been found not to differ notably from those of the remainder of the series. Thus among the original 47 patients diarrhoea had been present for a mean duration of 3¼ months; among the 17 whom it has been possible now to trace, diarrhoea had originally been present for a mean duration of three months. Tongue lesions, including glossitis, with inflamed and atrophic mucosa and ulceration, were present in 12 of the 17 now followed up, as compared with 39 of the 47 in the complete series. The average amount of weight lost among the 17 now followed up was 21 lb. (9.5 kg.), as compared with 28 lb. (12.7 kg.) for the complete series. The mean haemoglobin values of the original 47 patients and of the 17 now followed up were respectively 12.2 and 11.9 g. per 100 ml. The faecal fat in those now followed up averaged 32.6 g.% of the faecal dry weight, compared with 37.1 g.% among the original 47 patients.

Present Condition of the Patients now Followed Up

Capacity for Work.—All 17 patients reported that they were able to carry on their full work. Their employment varied widely; nine were doing sedentary work, four were on moderately heavy work, and four were employed on heavy manual labour.

Weight.—Since returning to the United Kingdom in 1944–5, 15 of the 17 had gained in weight, the average gain being 11 lb. (5.0 kg.); the remaining two had each lost 1½ lb. (680 g.).

Diarrhoea.—Since their condition was reviewed 10 years ago, 11 of the 17 patients had been completely free from diarrhoea, three have had single attacks lasting 48 hours during these 10 years, another has had a single attack lasting 96 hours, one has had occasional attacks lasting 24 to 48 hours, and one states that he has had many attacks lasting 48 to 72 hours. All state that normally they pass one to two stools a day and that the faeces are formed, inoffensive, and of normal colour and size.

Glossal Ulceration.—Three of the 17 had had some glossal ulceration during the past 10 years. Two had had one or more ulcers of the tongue present for 2 to 10 days and associated with attacks of diarrhoea; the third patient had had a buccal ulcer lasting for two to three days on one or two occasions during this period.

Appetite.—Three patients reported that they still have a disinclination to eat fatty or fried foods, but the remaining 14 stated that their appetite was normal and good.

Abdominal Discomfort, Distension, and Flatulence.—Two patients stated that a minor degree of these symptoms has been present almost continuously throughout the past 10 years, and a third stated that they occurred after ingestion of fatty and fried foods. These symptoms, however, have not been severe enough to limit the patients' activity in any way, and in view of their subjective nature their connexion with the original sprue is doubtful. Similar considerations also applied to two patients who still complained of lassitude after undue exertion but who nevertheless were able to carry out their full work. No patient now complains of cramps.

Discussion

If the 17 patients recently followed up are representative of the whole series—and there is no reason to believe that they are not—then it appears that the long-term prognosis in tropical sprue is good and that after treatment with a high-protein, low-fat diet a patient may be expected to be restored to full health. Alimentary symptoms, except possibly glossal ulceration, in such patients appear to be no more frequent than is to be expected among persons who have not had sprue. Those followed up in this study have been living on a normal diet without any restriction on consumption of fats, so that in tropical sprue protracted dietary limitation appears to be unnecessary.

All the 17 patients were treated before the introduction of folic acid or vitamin B_{12}, and thus their satisfactory return to health demonstrates that, at most, administration of large amounts of these substances shortens the illness but that they are not essential to recovery. This observation emphasizes a difference between sprue as encountered in the East and that reported in the Caribbean region, where folic acid and/or vitamin B_{12} have been used extensively for treatment and they or liver extract may be essential for it. Woodruff (1952) drew attention to these differences, particularly to the severe degree of anaemia usual in Caribbean cases and to the common absence of reference to steatorrhoea in reports on sprue from this region. He suggested that the condition commonly described there as "sprue" is nutritional megaloblastic anaemia, with which some alimentary symptoms may be associated and thus be a source of confusion. The satisfactory recovery without the aid of specific haematinics of the patients here followed up further supports this view.

The chronicity of idiopathic steatorrhoea or non-tropical sprue and its failure to be influenced other than temporarily by treatment indicate, firstly, that assessment of the history and/or observation following a period of treatment afford valuable means of differentiating between tropical sprue and idiopathic steatorrhoea, for patients with the former will recover and remain well, while those with the latter will not. Secondly, the difference in course between the two conditions suggests that they are separate aetiological entities; tropical sprue being characterized by a temporary upset in bowel function and in fat absorption, whereas in idiopathic steatorrhoea or non-tropical sprue this upset is permanent. By means of jejunal biopsy, Shiner (1956, 1957), Doniach and Shiner (1957), and Sakula and Shiner (1957) have demonstrated that in idiopathic steatorrhoea mucosal atrophy is present, and a permanent change of this kind with loss of enzyme function in the tissues affected and a similar temporary disturbance in tropical sprue, perhaps secondary to changes in the intestinal bacterial flora, might well account for the difference in course and in prognosis of these two conditions.

Summary

Doubt concerning the prognosis of tropical sprue has arisen probably through confusion between it and idiopathic steatorrhoea or non-tropical sprue, which, it is generally agreed, is a relatively chronic disorder. The prognosis of tropical sprue has therefore been studied by following up patients who contracted it in India and Burma during the 1939–45 war and who were invalided to Britain. It has been difficult to contact the patients because so many of them have changed their residence several times or have emigrated since 1945. Of 34 patients followed up, however, three years after invaliding, it has now been possible to contact 17. It is appreciated that there are pitfalls in drawing conclusions from so small a proportion of the original number of patients, but they are believed to be representative: it is known, for example, that several emigrated in good health.

Those contacted have all been found to be in good health, to be carrying on their full work, and to have gained an average of 9½ lb. (4.3 kg.) in weight. Attacks of diarrhoea, glossal ulceration, abdominal discomfort, and distension have been infrequent.

The long-term prognosis of tropical sprue appears to be good and to contrast favourably with that of idiopathic steatorrhoea. This contrast in course affords one means of differentiating the two disorders and suggests that they are separate aetiological entities.

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CONTROLLED HYPOTHERMIA

RECENT DEVELOPMENTS IN THE USE OF HYPOTHERMIA IN NEUROSURGERY

BY

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Hypothermia is a technique of comparatively recent application, and may be described as a method of reducing the normal body temperature of the whole patient. The method was first practised by Smith and Fay (1939) in the attempted treatment of neoplasms, with a view to slowing the rate of tumour growth at lowered temperatures.

More recently McQuiston (1949) used hypothermia during cardiac surgery carried out on hypoxaemic children. Further interest was taken in this when Bigelow *et al.* (1950) suggested that the lowered oxygen demand of the brain during hypothermia would protect it against ischaemia during intracardiac operations. Since then the method has been used extensively as an aid to cardiac surgery.

The application of hypothermia to neurosurgical conditions is of more recent origin. Rosomoff and Gilbert (1955) noted a reduced brain volume when experimenting with dogs under hypothermia, and accordingly recommended its use in neurosurgery. Lougheed *et al.* (1955) followed with a report on two cases in which hypothermia had been used for the surgical treatment of vascular lesions, and Botterell *et al.* (1956) reported on the use of hypothermia in the management of 22 cases of intracranial aneurysms.

The Investigation

Thus the value of hypothermia in the treatment of neurosurgical conditions had been established on a broad basis by the end of 1956, when work was begun with a view to developing a practical and routine method for use with a busy neurosurgical unit.

From November, 1956, until December, 1957, 123 patients whose ages ranged from 6 to 78 years were treated under hypothermia. This paper shows how the routine method was evolved and established.

At the outset an unselected series of ruptured intracranial aneurysms and angiomas were treated surgically under hypothermia; later, when it became evident that the method was safe and the value of the improved operating conditions was appreciated, confidence grew, and the method was used during other intracranial procedures, particularly for meningiomas.

The danger of repeated subarachnoid haemorrhage in cases of ruptured intracranial aneurysms is well known. Thus to avoid a further bleed before operative treatment could be carried out, and also in the hope that the patient's condition might improve, the first five cases in this series were cooled over a period of 5 to 19 hours, using the "lytic cocktail" combined with sodium amylobarbitone to prevent shivering. Fans played upon the patient continuously and body surfaces were kept constantly moist with a dilute solution of cetrimide in water, the former being added to reduce surface tension, thus allowing a film of moisture to remain on the skin for a longer period than would water alone. At the time chosen for operation the temperature lay between 30 and 31° C., and a general anaesthetic was then given. This was discontinued at the end of the operation, when warming was begun with electrically heated blankets. This method has the following disadvantages:

1. Shivering occurred even though large amounts of drugs were administered. In one case 180 mg. of chlorpromazine, 100 mg. of promethazine hydrochloride, 190 mg. of pethidine, and 900 mg. of sodium amylobarbitone were given and slight shivering was still present, which increased if the patient was moved or disturbed in any way. Rosomoff and Gilbert (1955) pointed out the need for adequate anaesthesia in these cases because of the rise in C.S.F. pressure which occurs with shivering.

2. As a result of the large quantities of drugs administered the blood pressure was not easy to control. A steep drop in blood pressure was apt to occur on moving the patient, on tilting to a head-up position, and again after only a small blood loss. This fall was not compensated for immediately, and the blood pressure tended to remain low for long periods. This reduced blood flow to the already damaged brain, which, even though the temperature was low and the tissue oxygen requirements were diminished, might well have proved to be insufficient. There was also considerable danger of cerebral thrombosis if the blood pressure remained low for any length of time.

3. The fall in temperature was difficult to control, and a further fall tended to occur after induction of general anaesthesia.

In view of the foregoing difficulties it was decided to take advantage of the strong anti-shivering action of nitrous oxide, as described subsequently by Parkhouse (1957).

Accordingly the sixth case in the series—a ruptured intracranial aneurysm—was treated by hypothermia under prolonged general anaesthesia. When the temperature had reached the required level the nitrous oxide was discontinued, and the effect of this, together with its reintroduction, is illustrated in Fig. 1. The pulse rate rose, and the blood pressure rose steeply as shivering became more marked, and both settled dramatically to their former level when the nitrous oxide was reintroduced. A slow rise in temperature occurred later as a result of the increased heat production on shivering, and further cooling was necessary to reduce the temperature to the required level again. Intravenous drugs were given during the initial cooling process—thiopentone 250 mg., pethidine 60 mg., "tubarine" 30 mg., sodium amylobarbitone 500 mg. in all were given. No further drugs were needed to prevent shivering after reintroducing nitrous oxide.

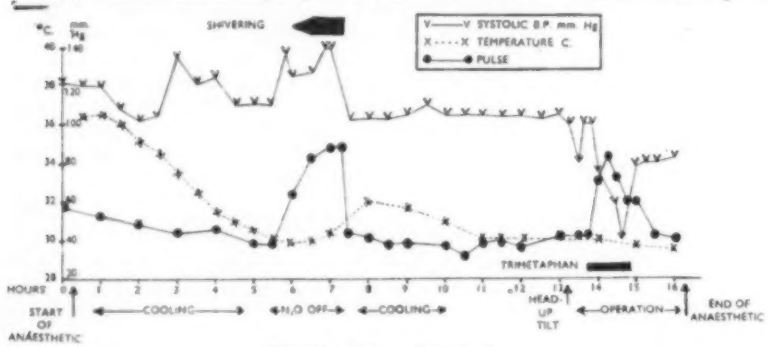

FIG. 1.—Chart of Case 6.

This case was of interest because the patient had undergone haemorrhage from a ruptured posterior cerebral aneurysm on four separate occasions during the three weeks prior to admission to hospital, the last haemorrhage

occurring within the 24 hours before admission. Further rupture was prevented by ligation of the neck of the aneurysm at operation, and the patient eventually made a complete recovery.

It became evident that the advantage of prolonged hypothermia, preventing further haemorrhage, did not outweigh the disadvantages of prolonged anaesthesia, and therefore the remaining cases were operated upon as soon as the temperature had been reduced to the required level under general anaesthesia.

The following method of producing a state of hypothermia at a temperature level between 31 and 30° C. was used for the remaining 117 cases.

Procedure

Anaesthesia

The patient was given promethazine, pethidine, and atropine as premedication. One hour later anaesthesia was induced with thiopentone, suxamethonium, and pethidine, and was maintained with nitrous oxide and oxygen, together with additional doses of pethidine and thiopentone. If this proved insufficient to prevent shivering, suxamethonium was given in repeated intravenous injections, or, alternatively, tubarine was given in small doses until shivering was controlled. Respirations were aided or controlled as required.

Hypothermia

Hypothermia was effected by means of surface cooling, using ice, after the induction of anaesthesia. Ice packs were placed above and below the trunk of the patient, and also over the large arteries which run near the surface of the skin—that is, the carotid, femoral, and axillary arteries. In order to avoid too great a drop in their temperature the limbs were not cooled directly. The skin in contact with the ice packs was massaged at frequent intervals to assist the circulation of the cooled blood; this was of particular value in the case of the obese patient, as it reduced the temperature gradient between the centre and the surface of the body.

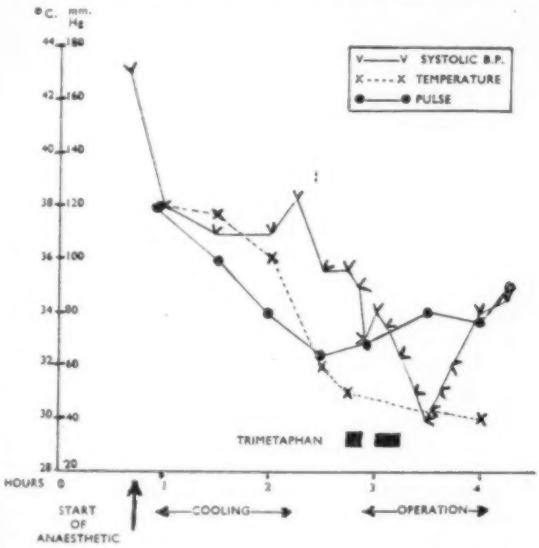

FIG. 2.—Chart of a thin patient (approximate weight, 57 kg.).

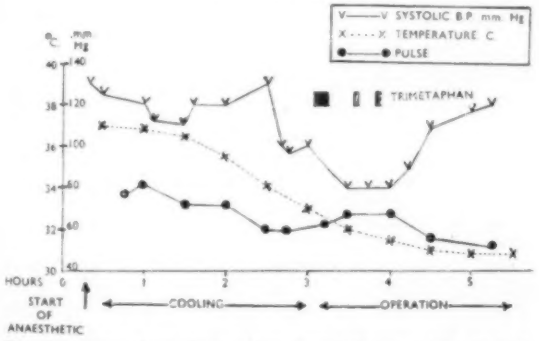

FIG. 3.—Chart of an obese patient (approximate weight, 73 kg.).

The main difficulty was to obtain toleration of the cold applied without depressing the vital centres or producing apnoea by giving large doses of relaxants: the temperature of the surroundings was found to be of little importance when ice was used, provided the ice was replaced as it melted. As the blood supply to the damaged brain had already been reduced by spasm of the supplying vessels, and would be further reduced by hypotension, care was taken not to depress the blood pressure until this was required during operation. Apnoea was produced during the process of cooling in those cases where relaxants were necessary to control shivering, but it was essential to ensure that respirations were present during the neurosurgical procedure, as a guide to the surgeon.

The ice packs were removed at 33–32° C., and the patient was then ready for operation. Before the main part of the operation had been completed the temperature had continued to fall to 31–30° C., 30° C. being the lowest temperature level required.

This further drop in temperature after the removal of the ice occurred more quickly and to a lower degree in the thin patient than in the obese, because of the insulating effect of fat against cold. Hence the steeper the fall in temperature during cooling the greater the "after-drop" expected. Thus when a thin patient was cooled rapidly the ice had to be removed at between 34 and 33° C. to avoid too profound a final drop in temperature. This point is illustrated in Figs. 2 and 3.

Temperatures

Rate of Temperature Fall.—When hypothermia was produced by the method described, the time taken for the temperature to fall was proportional to the weight and surface area of the patient. As a rough guide, the time taken for the temperature to fall from normal to 33° C. (when the ice was removed) was calculated on the basis of one hour per 6 stone (38 kg.) weight. Thus a 12-stone (76-kg.) patient would take approximately two hours, the time varying slightly according to the patient's surface area—that is, the tall and thin would take a relatively shorter period than shorter patients of the same weight.

Temperatures were recorded from the rectum and from the nasopharynx, using glass alcohol thermometers. In 28 cases the brain temperature was also recorded during operation, and Table I shows the variable degree of correlation of the rectal temperature compared with the brain temperature.

Nasopharyngeal temperatures were not recorded during operation, as access to the nose, using glass thermometers, was impossible.

TABLE I

Case No.	Weight in Kg.	Temperature (°C.)		Case No.	Weight in Kg.	Temperature (°C.)	
		Rectal	Brain			Rectal	Brain
1	63	32	32·2	15	67	31·4	29·4
2	94	31·6	30·7	16	82	31·4	29·4
3	63	29·5	30·1	17	63	31·2	29·8
4	63	32	29·8	18	57	31	28·9
5	63	31·5	29·6	19	57	30·4	31·2
6	70	29·4	29·2	20	60	31·2	30
7	50	30·5	28·9	21	82	32	30
8	60	31·2	30·9	22	70	30·5	29·5
9	111	35·2	33·1	23	63	29	28·9
10	63	31	29·2	24	50	30·9	29·1
11	79	31	30·9	25	63	33	30·4
12	94	32·5	31·4	26	63	34·3	33·1
13	57	30·7	30	27	63	30·8	30·4
14	63	30·5	30·2	28	57	30·4	29·8

Warming

At the end of the operation anaesthesia was discontinued, and no active attempts were made to rewarm the patient unless the temperature tended to drop post-operatively. Normal temperatures were usually regained within eight hours of the operation. Promethazine was given to reduce shivering, and, if the patient was conscious and complaining of cold, pethidine was given. Consciousness was regained at low temperature in cases where brain damage had been minimal and anaesthesia had been light; one patient was capable of answering questions at 29.5° C.

The rate of temperature rise post-operatively gave an indication of the neurosurgical state of the patient. If brain damage had been slight there was a rapid rise within a period of three to five hours, but when brain damage had been severe the temperature would take as long as two to three days to reach normal, with little or no shivering occurring. This slow rise in temperature in the very sick was of definite advantage, as the oxygen requirements of the brain remained low for a long period.

Blood Pressure

The common pattern of the blood pressure is illustrated in Fig. 4. The initial fall after induction of anaesthesia was followed by a rise due to vasoconstriction of the peripheral vessels, as a result of cooling. This was followed by a gradual fall due to diminished cardiac output, which was

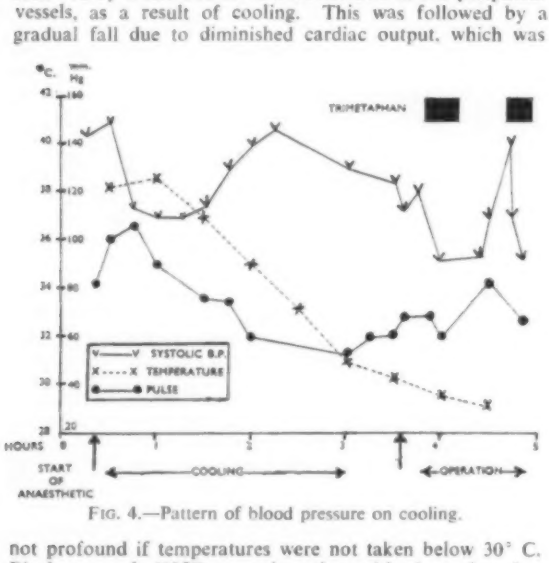

FIG. 4.—Pattern of blood pressure on cooling.

not profound if temperatures were not taken below 30° C. Bigelow *et al.* (1950), experimenting with dogs, found a similar pattern in blood pressure on cooling.

With this method of hypothermia, the blood pressure was little disturbed on moving the patient. All operations were carried out with the patient lying with a head-up tilt.

In the first six cases described, this tilting produced falls in blood pressure of between 20 and 80 mm. Hg, whereas using the second method the fall was rarely more than 10 mm. Hg, thus giving greater control over the blood pressure.

This was an advantage, because, although it is safer at low temperatures to lower the pressure due to diminished oxygen requirements (Dundee *et al.*, 1954), it was considered advisable in these cases of brain damage with spasm of the cerebral vessels to limit this low pressure to the shortest time possible.

Thus the blood pressure was lowered only when necessary by using trimetaphan camphorsulphonate ("arfonad").

Trimetaphan Camphorsulphonate

Operations were performed in nearly all cases at a blood-pressure level of 70–80 mm. Hg. Trimetaphan was given by intravenous infusion at a concentration of 1 mg./ml. normal saline. In common with other drugs trimetaphan takes longer to act at low temperatures. The sensitivity of patients to this drug varied at low temperatures as at normal temperatures, and consequently time had to be allowed to assess the sensitivity of the patient to the drug by giving it at a very slow drip-rate for three to five minutes. If this was not done a profound drop in blood pressure would occur when the trimetaphan took effect on a sensitive patient. This profound drop in pressure might be prolonged because the compensatory mechanisms for hypotension do not act normally at low temperatures. Prolonged diminished blood supply to the damaged brain might thus occur.

The total amount required to maintain hypotension was found to vary as much in cold patients as in patients at normal temperatures, and large amounts of trimetaphan

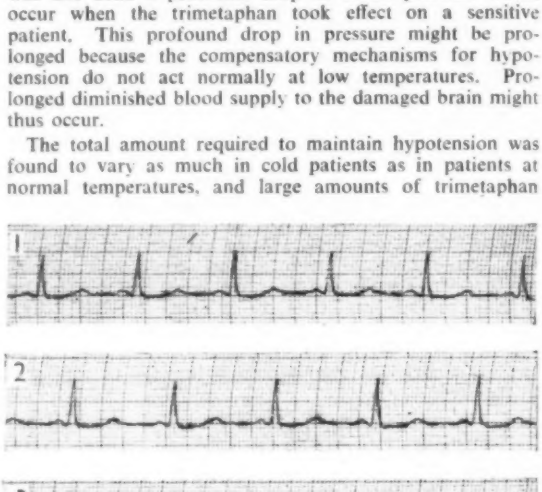

FIG. 5.—Showing effect of trimetaphan. (1) Lead II. Temperature, 30.8° C.; blood pressure, 95 mm. Hg. (2) Lead II. Temperature, 30.8° C.; blood pressure, 60 mm. Hg with trimetaphan. (3) Lead II. Temperature 30.8° C.; blood pressure, 60 mm. Hg; trimetaphan discontinued.

(200 mg. or more for a period of one to two hours during operation) might be necessary.

Trimetaphan was given in 74 of the 123 cases, and was effective in all but one of them. In every case there was a slight rise in the pulse rate, usually 10 to 20 per minute, even at temperatures just below 30° C. In the one resistant case a drop of only 5 mm. Hg could be obtained at a temperature of 29° C; whereas the pulse rate rose from 48 to 130 a minute and returned to 80 a minute a quarter of an hour after trimetaphan had been discontinued.

It was observed that a fall in blood pressure was difficult to obtain when the brain underwent retraction, and at low temperatures retraction of the brain caused a marked rise in blood pressure when trimetaphan was not being given.

Fig. 5 shows the electrocardiogram at a temperature of 30.8° C. when trimetaphan was given to lower the blood pressure from 95 to 60 mm. Hg.

Some Findings

Blood Loss.—At low temperatures patients did not compensate well or quickly for loss of blood. This was shown by the almost immediate drop in pressure, while there was little or no rise in pulse rate. A loss of only 250 ml. of blood could cause a severe drop in blood pressure, which did not return to the original level even when blood was replaced. If flattening of the operating table was not effective, small intermittent intravenous injections of noradrenaline, combined with blood replacement, were given to raise the blood pressure.

Pulse.—Increasing bradycardia occurred as the temperature fell; usually the rate was below 60 a minute at 30° C. The lowest value obtained was 36 a minute. Atropine, 0.3–0.4 mg., was given intravenously if the rate dropped below 50 a minute. This usually, but not always, caused

an increase in the pulse rate, which gradually fell again. The cases which did not respond by an increased pulse rate were those in which the sino-auricular node was directly depressed by the effect of cold (Cookson and Di Palma, 1955). Irregularities of the pulse were encountered during cooling, but these remained for only short periods. Moving the patient was the most common cause of these irregularities, which often appeared when transferring the patient from the operating table after anaesthesia had been discontinued: the pulse became regular again after a rise in temperature of a few degrees. Thus moving the patient under light anaesthesia should be avoided. Auscultation of the blood pressure always became difficult as the temperature fell, owing to vasoconstriction of the vessels. The radial pulse could be palpated throughout hypothermia in all but three cases. To reduce the vasospasm in these three cases, a stellate ganglion block was performed at the beginning of the operation, which proved effective in each case. Thus it was possible to keep a record of the systolic blood pressure by palpation of the radial pulse in every case.

Electrocardiographic Control.—The one almost constant finding, apart from lengthening of the whole complex, was the appearance of the "Osborn effect" (Osborn, 1953). This is a secondary wave closely following the S wave—so closely that it appears to be part of the QRS complex. Osborn looked upon this finding as a bad prognostic sign, as it usually preceded fibrillation by about half an hour. G. R. Graham (1957) pointed out that this change in the electrocardiogram under hypothermia is almost constant, and of no serious significance. This was found to be true in this series of cases.

Respirations.—Respirations were controlled, or aided as necessary, with a high flow of gases (4 litres of oxygen to 6 litres of nitrous oxide) without absorption of carbon dioxide. Respirations could not be controlled during operation because their presence and character were a valuable guide to the surgeon. Thus large doses of relaxants for abolishing shivering could not be used. The respiratory rate fell with the temperature in every case. The operation of clipping the anterior cerebral artery in the treatment of anterior cerebral aneurysm at normal temperatures sometimes produces apnoea which appears almost immediately the artery has been occluded. This apnoea was also produced at low temperatures, but might take five to six minutes to appear after the artery had been clipped. One case remained apnoeic for 30 minutes, after which time breathing restarted. Neither this case nor other cases of apnoea from the same cause under hypothermia suffered any lasting ill effect.

Operating Conditions and Selection of Cases

Haemorrhage from the scalp was usually reduced, but in 5 of the 123 cases haemorrhage was greater than at normal temperatures, and it was concluded that the process of cooling had probably interfered with the effective clotting of blood in these cases. Haemorrhage inside the dura was reduced in all cases, including the five which had increased scalp bleeding.

Intracranial tension was lower than normal in 97 of the cases operated upon, normal in 15, and raised in 8. Some of the 97 cases had large intracranial clots, and the tension was low only after these had been removed.

Vascular spasm of the cerebral vessels was present in many of these ruptured intracranial aneurysms at normal temperatures, as demonstrated by the arteriogram. This condition was not abolished by hypothermia, as spasm of these vessels could also be demonstrated at temperatures of 30–31° C.

Selection of Cases.—Operation took place as soon after admission as possible, and no patient was considered too ill for surgery. Many were already dying from the effects of the haemorrhage they had recently suffered; such cases were classified as category A, and the remaining cases were divided into categories B and C according to the length of time since the last bleed from the aneurysm. There were 29 moribund patients, of whom 16 died in spite of treatment. These cases were unselected both from the neurosurgical and the general condition. Among this series were many chronic hypertensive patients and many with left ventricular hypertrophy and coronary disease. There were two cases of diabetes mellitus and two cases of syphilitic aortitis, one of which had a ruptured aortic valve and was at the time under treatment for cardiac failure.

Post-operative Complications

Bronchopneumonia was a problem in all cases of continued coma or drowsiness, and particularly if there had been pre-operative signs of chest infection. Antibiotics were given to all cases undergoing hypothermia.

Tracheotomy was performed in every case of continued coma to facilitate suction of secretions from the trachea and bronchi.

There was one case of pulmonary embolus, one of deep calf-vein thrombosis, and one of thrombosis of the long saphenous vein as a result of the intravenous infusion.

Seven cases were reopened post-operatively. In five of these only cerebral oedema was found, and the remaining two cases had subdural haematomata.

Ice was used in packs directly in contact with the skin in 117 cases, and no post-operative damage to the skin occurred in any of these cases.

Summary of Results

The results obtained are shown in Table II.

TABLE II

	No.	Died
Category A aneurysms	29	16
Categories B and C aneurysms	60	12
Angiomas	10	2
Meningiomas	13	None
Primary intracerebral haemorrhage	2	2
Head injuries	3	2
Pituitary tumours	2	1
Gliomas	2	None
Acute subdural	1	None
Excision of abscess capsule	1	None

No deaths occurred during the process of hypothermia or during operation. Many of the deaths occurred weeks or even months after operation.

Summary and Conclusions

The method of producing hypothermia described was evolved from the treatment of 123 cases, 117 of which were treated by surface cooling, using ice, which has the following advantages: (1) it is simple to operate in so far as the minimum of assistance and of complicated equipment are required; (2) control is good, because the time to cool can be predicted; and (3) only a limited number of drugs are necessary.

During the whole of the series no death occurred that was directly attributable to the use of hypothermia, and it is therefore concluded with some certainty that, provided the body temperature is not lowered below 30° C., the improved operating conditions produced by hypothermia may be obtained at a small increased risk, when compared with the use of a general anaesthetic alone.

In view of this, hypothermia was later used successfully for other intracranial procedures, such as angiomas and meningiomas, where the improved operating conditions were considered to be of value.

This procedure has become routine for all such cases at the Atkinson Morley's Hospital, where this work was undertaken.

I thank the consultants and all members of the staff of the Atkinson Morley's Hospital for their help and co-operation in conducting this research work, which was made possible by a Research Fellowship awarded by St. George's Hospital.

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PREVENTION OF RHEUMATIC FEVER RECURRENCES

BY

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Sulphonamides were first used in the prevention of rheumatic fever recurrences nearly 20 years ago (Coburn and Moore, 1939; Thomas and France, 1939). In 1941, Thomas, France, and Reichsman published their results in a controlled series that had been followed for four years. They found that the frequency of throat cultures positive for Group A haemolytic streptococci was less in a group of 55 patients protected by daily sulphanilamide and that none in this group had had acute streptococcal throat infections or further attacks of rheumatic fever. In the control group (67 patients) there were 15 major attacks of rheumatic fever and four deaths. Rosenberg and Hench (1946) summarized the results of 10 controlled series published between 1939 and 1946, involving over 1,000 person-seasons in each of the two groups: the recurrence rate in the protected series was 2.2% per patient-season and in the unprotected 13.7%.

In 1947 Burke published the first results with penicillin. One group of 10 patients had been given 1,500 Oxford units by mouth daily, and another group of 10 were studied as controls: both had been followed for one year after discharge from hospital. There was a higher incidence of infection of the upper respiratory tract in the unprotected group, and one relapse occurred in this group but none in the protected. There have been many American studies in the past 10 years (summarized by Stollerman, 1954), but only few from this country. Pitt Evans (1950) gave 100,000 units of penicillin daily by mouth to one group of 155 children in a convalescent home; another 145 children were studied as controls. Both groups were followed as in-patients for an average period of 22 weeks. The incidence and duration of the Group A haemolytic streptococcal carrier state was approximately four times greater in the unprotected than in the protected group, and clinical pharyngitis and tonsillitis was over seven times more frequent. There were no relapses of rheumatic fever in the 155 protected patients and four in the 145 unprotected. Gale *et al.* (1952) observed 73 patients for eight months after discharge from hospital: 41 were given 200,000 units of penicillin daily: the remaining 32 received lactose and glucose. Throat swabs were taken every two weeks. There was a lower incidence of positive throat cultures in the treated group, and, whereas two rheumatic relapses occurred in the 32 controls, there were none in the 41 treated.

Prophylaxis was not used on any large scale in this unit until 1951. We relied instead on isolation (and, if necessary, treatment) of all new admissions until their throat cultures were known to be negative for haemolytic streptococci, and on weekly throat-and-nose swabbing of all patients and staff; anyone with a positive throat swab was isolated and given intramuscular penicillin. In this way the number of streptococcal infections was kept at a very low level and the recurrences in hospital were few. Experience in this country indicated that recurrences of rheumatic fever *after* discharge from hospital were much less frequent than had been reported in the U.S.A., where estimates ranging from 40% per year (Wilson and Lubschez, 1944) down had been reported. Up to 1951, therefore, in view of possible toxic effects from long-continued administration and of the low recurrence risk, our patients had not been put on to prophylaxis on discharge from hospital.

Present Investigation

In the years 1949 and 1950 there were 96 patients in this unit who were diagnosed as having rheumatic fever; none were put on to prophylaxis in hospital. All fulfilled the criteria for diagnosis of rheumatic fever as defined by Duckett Jones and modified by the American Heart Association (1955). They had, therefore, either two major and one minor, or one major and two minor, criteria (major criteria: polyarthritis, chorea, nodules, erythema marginatum, and carditis; minor criteria: fever, arthralgia, prolonged P–R interval, raised sedimentation rate, evidence of preceding haemolytic streptococcal infection or previous history of rheumatic fever or rheumatic heart disease). Four patients died in hospital. The remaining 92 were not put on to prophylaxis at the time of discharge from hospital. They were seen for follow-up examination at three-monthly intervals for the first year, and thereafter once each year. At each examination a careful history was taken, with special reference to sore throats and limb or joint pains; a complete physical examination was carried out; and blood was taken for sedimentation rate. All 92 were seen at one year, 91 at two years (1 defaulter), 89 at three years (3 defaulters), 87 at four years (4 defaulters and 1 patient who had died in a recurrence at three years), and 85 at five years (2 more defaulters). Thus there were six defaulters by the fifth year and one had died at three years.

In view of the mounting evidence of the efficacy of prophylaxis and the low incidence of toxic reactions, we started to use prophylaxis as a routine measure for both in-patients and out-patients in 1951 as stipulated in the U.S.–U.K. treatment trial in which we were participants (Co-operative

TABLE I.—*Comparison Between Protected and Unprotected Groups on First Admission into Hospital*

Group	Total No.	Sex		Age in Years on Admission		Degree of Carditis on Admission			Duration of Disease Activity on Admission in Days		
		M	F	0–10	11–16	None	Pres. 1st Attack	Pres. 2nd or Later	0–14	15–43	43+
1949–50 (unprotected)	96	53	43	46	50	28	42	26	50	22	24
1951–52 (protected)	88	44	44	38	50	13	49	26	30	32	26

Clinical Trial, 1955). In the years 1951 and 1952, 88 patients were admitted with rheumatic fever, all of whom fulfilled the same diagnostic criteria as the previous group. The two groups were also similar as regards age and sex incidence, degree of heart involvement, and duration of disease before admission (Table I).

All 88 patients admitted in 1951 and 1952 were given prophylaxis in hospital (tablets containing sulphathiazole, sulphadiazine, and sulphamerazine ("sulphatriad"), 1 g. daily). Two patients died in hospital. In the remaining 86 prophylaxis was continued after discharge. These 86 patients were seen for follow-up examination at six-monthly intervals for the first two years and thereafter once each year. They were interrogated and examined in the same way as the previous group, and blood samples were taken for packed cell volume, sedimentation rates, and anti-streptolysin O titres. Urines were also tested for sulphonamide (La Rosa, 1945). 85 were seen at one and two years (1 defaulter), 81 at three years (5 defaulters), 79 at four years (6 defaulters), and 71 at five years (6 defaulters and 9 not yet due for follow-up).

Results

Recurrences were defined as further episodes of rheumatic activity after discharge from hospital in which the criteria for diagnosis were again fulfilled—that is, there were two major or one major and two minor criteria. None had more than one recurrence in any 12-months period.

In the unprotected group of 92 patients admitted between 1949 and 1950, 18 patients had recurrences during the first five years of follow-up. 17 of them had further attacks of rheumatic fever: 14 had one such attack, 2 had two, and 1 had three. Thus the 17 patients had a total of 21 recurrences. The remaining patient had three attacks of chorea. There were therefore 24 episodes of fresh rheumatic activity. Of the 86 in the protected group, 5 had further attacks of rheumatic fever.

Table II shows the number of recurrences in the two groups at or before each annual follow-up. In the unprotected group, 9 of the 17 with recurrences of rheumatic fever were put on to prophylaxis during their readmission to hospital; none of them had further attacks. These cases have therefore been excluded from the "number at risk" after their discharge from hospital, as they were then receiving prophylaxis. At one year there were 92 unprotected "at risk"; at two years 90 (1 defaulter and 1 on prophylaxis); at three years 86 (3 defaulters and 3 on prophylaxis); at four years 81 (4 defaulters, 1 dead at three years in a recurrence, and 6 on prophylaxis); and at five years, 77 (6 defaulters, 1 dead, and 8 on prophylaxis). In the protected group, 85 were seen at one and two years (1 defaulter at each); 82 at three years (5 defaulters); 79 at four years (6 defaulters); and 71 at five years (6 defaulters and 9 not due for follow-up).

TABLE II.—*Number of Recurrences Per Year at Annual Intervals in Cases that Survived*

Years from Admission:	0	1	2	3	4	5
Unprotected group:						
No. at risk	92	92	90	86	81	77
,, of recurrences ..	—	5	6	5	4	4
% ,, ..	—	5·4	6·7	5·8	4·9	5·2
Protected group:						
No. at risk	86	85	85	81	79	71
,, of recurrences ..	—	1	1	0	2	1
% ,, ..	—	1·2	1·2	0	2·5	1·4

The mean incidence of recurrences per patient-year was 5.6% in the unprotected and 1.2 in the protected.

Discussion

Whilst the number of recurrences during the 12-months period after discharge from hospital was consistently and considerably less in the protected group, the reduction is less than reported in American series. This is because the recurrence rate in the unprotected was much lower than seems to be the usual experience in the United States. The total mean incidence of recurrences per patient-year in our unprotected group was only 5.6%. Wilson and Lubschez (1944), in New York, found an overall recurrence rate of 25% in children aged between 4 and 13, and Fischel's unpublished figures from another hospital in New York (quoted by Stollerman, 1954) showed that of 239 unprotected patients 43 (18%) had recurrences during the first year.

Such large differences in recurrence rate in unprotected populations may depend on different criteria for recurrences or on other factors. Thus, out-patient prophylaxis is less stringent and effective than in-patient prophylaxis. In our protected group, of the five that had recurrences, one was known to have stopped taking sulphonamide two months previously and in another it was probable that the drug had been discontinued. Under barrack conditions (and some of the American figures come from Service camps) the risk of contracting streptococcal infection is greater than in the home, and the attendance of patients for illness may be different in different countries. However, most of the American series seem to agree on a high incidence of recurrences in unprotected series of whatever age, while in the few series reported in this country the incidence has been low (Pitt Evans, 1950; Gale *et al.*, 1952; present series). This difference may account in part for prophylaxis being taken up less enthusiastically in this country than in America.

Although the two groups of cases in this series were not run concurrently, the five-year period of study overlapped by two to four years in the two groups. In both groups the recurrence rate was similar during each of the five years of follow-up. This is of considerable interest, for Wilson and Lubschez reported that the risk of recurrences in the year following an attack was 38.7%, whereas the risk after one year's freedom from attacks was only 11.7%. In our series the recurrence rate has remained at a similar level throughout the five-year period despite the fact that the children were getting older and were further from their initial attack. Furthermore, Wilson and Lubschez found an overall recurrence rate of 25% in children aged 4 to 13, and only 9% in those aged 14 to 16. In our unprotected cases the age distribution on admission to hospital was 46 patients up to and including the age of 10, and 50 between 11 and 16. Of the 46 up to and including the age of 10, 7 had recurrences; of the 50 aged between 11 and 16, 10 had recurrences. There is manifestly no great falling off of recurrence rates after puberty.

Objections that have been raised to prophylaxis have been discussed in a previous publication (Bywaters *et al.*, 1957). Among these have been the fear of toxic reactions (agranulocytosis, drug rashes, and renal damage) and of streptococcal resistance to sulphonamide. In this series, though patients were given sulphonamide over periods of four and five years, such reactions were few. Two in the protected group complained of lassitude during the first year after discharge. One, a girl of 12, was found to have a white blood cell count of 3,850 per c.mm. with 25% polymorphs. She was admitted to hospital and sulphonamide prophylaxis was changed to penicillin. One week later she had recovered: the white-cell count was 7,450 per c.mm. with 70% polymorphs. The other, a boy of 5, had a white-cell count of 2,000 per c.mm. with 20% polymorphs at the sixth month follow-up. Penicillin prophylaxis was substituted, and, although the white-cell count remained low for some months before returning to normal, prophylaxis continued uneventfully.

No patient in this series developed agranulocytosis, although another of our patients (not included in this series because she was over the age of 16 on first admission) developed agranulocytosis at the eighth week; she responded satisfactorily to intramuscular penicillin. One patient in the series developed urticaria after 10 weeks on sulphonamide. The drug was stopped after four days and penicillin prophylaxis substituted. The rash persisted for another four days and then subsided. No instance of streptococcal resistance to sulphonamide was encountered,

though in another patient (not included in this series because he had chorea only) haemolytic streptococci resistant to sulphonamide were found in routine weekly throat swabs after eight weeks of treatment. The patient was treated with bactericidal doses of intramuscular penicillin, a tonsillectomy was performed, and prophylaxis was then continued with oral penicillin.

Since that time, all patients with rheumatic fever or chorea have been given sulphonamide or penicillin prophylaxis in hospital, and this has been continued after discharge (sulphatriad, 1 g. daily, or penicillin G, 200,000 units twice daily). Our original impression of the efficacy of this prophylaxis has been confirmed, and toxic reactions have been few in number and harmless. Most have occurred within a few weeks of starting treatment—that is, whilst the patients were still in hospital. Prophylaxis has then been changed from one drug to the other and there has been no further trouble.

We have no data available on differences in the recurrence rate between cases treated with sulphonamide and penicillin. Assuming both drugs to be equally effective, penicillin would be the one of choice, for there is the possible though small danger of agranulocytosis with sulphonamide. The slight extra cost of penicillin (3.6d. a day as compared with 1.6d. a day for sulphonamide) does not seem important, and storage of penicillin presents no problems, for the tablets retain their potency for three months if kept in an airtight tin in the cool. Injections of benzathine penicillin have been advocated by some as preferable to penicillin by mouth. Though this method ensures that prophylaxis is carried out, it is difficult to impose a regime of weekly injections on children in the knowledge that this must be continued for years. The Rheumatic Fever Committee of the Royal College of Physicians (1957) recommends 200,000 units of penicillin G twice daily, or 120 mg. of penicillin V twice daily, and that benzathine penicillin should be used if for any reason oral prophylaxis cannot be given. With this we concur.

Finally, for how long should prophylaxis be continued? This is a matter for individual judgment, taking into account parental attitudes and circumstances. It is our belief, based on these figures for recurrence rates, that prophylaxis should continue for at least five years after the last attack or until the child has left school, whichever period is the longer (Rheumatic Fever Committee of the Royal College of Physicians, 1957). If, after leaving school, patients are exposed to an increased risk of streptococcal infection—that is, should they enter a university or one of the Services—then prophylaxis should be continued for a further period. If liability to reinfection is based on M antibody level, it may be that even more prolonged prophylaxis will be necessary.

Summary

Two comparable groups of patients with rheumatic fever were followed for a period of five years. One group of 96, admitted in 1949–50, were given no prophylaxis either in hospital or after discharge. The other, comprising 88 patients admitted in 1951–2, were given 1 g. of sulphonamide daily in hospital and after discharge. The period of follow-up in the two groups overlapped by two to four years.

The mean incidence of recurrences per patient-year was 5.6% in the unprotected and 1.2% in the protected. There was only small variation from year to year in each group, and no tendency for the recurrence rate to decrease with time. The reasons for the relatively low incidence of recurrences in the unprotected group and other differences between this and American series are discussed. Toxic reactions were few: none were serious. The duration, dosage, and merits of various forms of prophylaxis (sulphonamide, oral penicillin, and long-acting penicillin by intramuscular injection) are discussed.

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DESENSITIZATION TO BEE STINGS BY INTRACUTANEOUS INJECTIONS OF WHOLE-BEE EXTRACT

BY

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Reports of more or less severe reactions to bee stings are not infrequent in South Africa, and deaths therefrom are occasionally reported in the lay press. Our own information about bee-sting sensitivity and the effects of bee stings derives largely from many physicians in various parts of the country who, describing more or less severe reactions in their patients, inquire about the possibility of prophylactic desensitization.

Persons sensitive to bee stings commonly manifest local reactions in redness and swelling at the site of the sting and general reactions in rash, urticaria, oedema of face and glottis, and often anaphylactic shock, with collapse, unconsciousness, and even death. There may also be malaise, vomiting, dyspnoea, or bronchospasm. These effects appear within minutes after the sting or reach their climax some hours later.

The majority of patients who show a high degree of sensitivity to bee stings have suffered symptoms of progressively increasing severity after each sting, following a longer or shorter period of freedom from significant reactions after the initial sensitizing sting, which may have been many years ago. The following examples are given in illustration:

A farmer 44 years old had frequently been stung, as a boy and young man, with more or less severe local reactions after each sting. When he was stung again in 1952 there was little local reaction, but within three minutes he became unconscious and remained so for two hours. On recovery he had a "choking" sensation, with headache and malaise continuing for a day or two.

A medical man with no family history of allergy was stung at the age of 3½ years by about a hundred bees. The stings were removed and he suffered no ill effects. When he was 12 years old he was stung on the hand and developed a swollen face. Two years later he was stung between the toes. This resulted in swollen eyes, oedema of the glottis, and extreme dyspnoea requiring urgent medical attention. At the age of 29 he was stung once on the forearm, and, although he was injected with adrenaline within 20 minutes and with three further injections at hourly intervals, he had to have treatment at hospital, where he was detained for some time. He was stung again 10 years later, and, although adrenaline was administered within 10 minutes, he developed alarming swelling of the face.

A physician wrote from the Transvaal: "A patient of mine was stung by a bee in the soft tissue around his eye and had a severe systemic reaction. He became semiconscious and vomited profusely; rapid heart, with fall of blood pressure. He had never been affected by a bee sting previously although stung many times."

As a result of our advice and recommendations concerning the possibility of desensitization, bee-venom extracts are

Details of 24 Persons Sensitive to Bee Stings Submitted to Desensitization.

Case No.	Sex and Age	Otherwise Allergic	Reactions from Bee Stings	Whole-bee Extract Skin Sensitivity and Treatment Series	After Desensitization: Reactions from Bee Stings	After Desensitization: Outcome
1	M 6	Urticaria from insect bites	Progressively more severe reactions from stings. Was stung recently and had to be treated with corticotrophin	1 unit 0·5–250 units	Stung twice during course of desensitization with hardly any effect from second sting	Successful
2	M 48	Migraine	For the past 2 years had developed palpitations, pallor, faintness, and prostration with every sting	50 units 25–500 units	Stung on finger: local oedema lasting only a few hours	,,
3	M 36	Vasomotor rhinitis from inhalation of mohair dust	Local swelling and severe itching, worse with each successive sting. General reaction not marked except slight swelling of eyelids and listlessness	500 units 250–2,000 units	Local spot only. No general reaction	,,
4	M 9	Not	Had become increasingly sensitive to stings. Last sting produced a marked local reaction and a very severe general reaction, including urticaria with oedema of glottis	1,000 units 500–3,000 units	Recently stung repeatedly with, at most, a slight local reaction. "This has been a most gratifying result"	,,
5	F 56	,,	Severe urticaria and palpitations	250 units 100–1,500 units	"Only mild reactions"	,,
6	M 5	,,	At age of 2 years was stung on face, gross oedema developing there. At age 4 was stung on left thumb and within a minute there was oedema of face with gross tachycardia, oedema of the larynx occurring 5 minutes later	250 units 100–1,000 units	After three separate stings on the one leg the only reaction was a local swelling	,,
7	M 32	,,	Stung at age 6 years and again at 13: no serious local reaction and no general effect. Recently stung by 5–6 bees on hands, with slight local swelling and itching of whole body 15 minutes later. Stung again 2 weeks later by 4–6 bees with slight local swelling but marked general itching and marked swelling of loose tissues of throat, eyelids, and armpits, with generalized urticaria and vomiting. "I firmly believe that I would have died from oedema of the throat and glottis if I did not inject myself with 1 ml. adrenaline immediately I realized that my tongue was getting thick." The patient is a physician	1 unit 0·5–25 units	Stung 6 months later on finger with only slight local swelling and itching	,,
8	M ?	,,	When stung on neck or face became pulseless, icy cold, and collapsed. Often found on ground by his family deathly pale after a single sting	500 units 250–1,500 units	Sting on arm: no untoward reactions	,,
9	F 41	,,	Always very sensitive to stings. Marked shock, breathlessness, fainting, and palpitations. The patient, a trained nurse living on a farm, gives herself adrenaline after a sting	250 units 100–1,500 units	Discontinued injections after 100 units owing to distance from doctor. Stung 9 months later, with only mild local erythema and no general reaction	,,
10	F 60	,,	Both grandmother and grandson reacted similarly to stings, with rash, tachycardia, and oedema of glottis. A sting in either patient meant an emergency call to the doctor	1,000 units 500–2,000 units	Only 6 injections of 500-unit extract. Stung 2 months later: no bad reaction	,,
11	M 3	,,		1 unit 0·5–25 units	No reaction after sting 2 months later or after sting one year later	,,
12	M 7	,,	Several episodes of anaphylactic shock with patient in very critical condition	50 units 25–3,000 units	No shock at all after recent sting	,,
13	M 50	,,	Severe anaphylactic type of reaction, with vomiting, urticaria, and collapse	500 units 250–2,000 units	After two recent stings only slight swellings. One sting on neck resulted in only mild flushing. "No doubt this man has benefited very considerably from desensitization. He is extremely happy at result"	,,
14	M ?	,,	Increasing sensitivity to stings. On last occasion, acute oedema of glottis and unconsciousness. The oedema developed so rapidly that he was unable to give himself an injection of adrenaline	5 units 2·5–3,000 units	Small urticarial weal at site of sting. No general reaction. "Naturally the patient is delighted"	,,
15	F ?		The physician provided a general account of five cases under his care. "Same history in each case: Patient feels unusually bad after first sting; after second sting, urticaria with slight oedema of glottis. One patient became unconscious by the time he reached hospital. Another was laying out a golf course and was seriously thinking of giving up his job owing to the increasingly severe reactions from bee stings"	50 units 25–500 units	"The injections were given according to the suggested dosages in the pamphlet accompanying the treatment extracts. Since desensitization all the patients can walk among bees with impunity"	,,
16	F ?			500 units 250–1,500 units		,,
17	M ?			500 ,, 250–1,500 ,,		,,
18	M ?			1,000 ,, 500–3,000 ,,		,,
19	M ?			1,000 ,, 750–2,500 ,,		,,
20	M ?	Vasomotor rhinitis. Also sensitive to grapefruit	Stung from childhood onwards with no effect at first, but later with progressively severe reactions. Recent stings resulted in swollen face, body rash, and "feeling of pins-and-needles in body"	1,000 units 750–3,000 units	Swelling of hands and arms continue, but no longer that "queer feeling" Patient feels that he is better after stings now	Some improvement
21	F 21	Not	Large areas of local erythema with massive swelling as well as general malaise and urticaria	10 units 5–100 units	Moderately severe local reaction with weal, urticaria, and swelling	Not successful

Continued overleaf

Details of 24 Persons Sensitive to Bee Stings Submitted to Desensitization—Contd.

Case No.	Sex and Age	Otherwise Allergic	Reactions from Bee Stings	Whole-bee Extract Skin Sensitivity and Treatment Series	After Desensitization	
					Reactions from Bee Stings	Outcome
22	M 43	Not	Twice stung in the past, with severe anaphylactic reaction each time	10 units 5 and 10 units only	Desensitization in June and July, 1953. Stung again in May, 1956, with bronchospasm and severe anaphylactic shock	Not successful
23	F 48	,,	Tachycardia, vomiting, and mental confusion within 2 minutes after a sting	10 units 5–100 units	Stung some months later; had nausea, vomiting, tachycardia, and body pains	,,
24	M 52	,,	After a sting he became mentally confused, dyspnoeic, intensely red in the face, and developed tachycardia and unconsciousness	1,000 units 500–1,500 units	A sting received 4 months later produced tachycardia, mental confusion, and collapse	,,

ordered for that purpose by physicians and are issued in a series of graded strengths referred to as "treatment sets." In this way, 50–60 treatment sets for desensitization purposes were issued annually in 1951–5, 86 sets in 1956, and 115 in 1957. These figures do not, of course, indicate the incidence of serious reactions to bee stings in the country, but merely reflect the spread of knowledge regarding prophylactic desensitization.

In our experimental and clinical studies extracts of whole bees have been employed instead of material from the sting apparatus, because our earlier investigations had shown that in persons sensitive to bee stings intracutaneous testing with extract of whole bee and with extract of sting-venom sac produced similar reactions, indicating, at least, the presence of a common antigen. From a practical point of view, in the large-scale preparation of extracts the removal of venom sacs with stings from large numbers of bees does not seem warranted when the preparation of the equally useful whole-bee extract is so simple.

Progressive skin tolerance to the injection of gradually increasing strengths of whole-bee extracts is the rule, and, as shown below, a parallel state of clinical hyposensitization is similarly attained.

Preparation of Whole-bee Extract

In the preparation of whole-bee extract many hundreds of bees are removed from the hive into a closed container, where they are killed with chloroform. The dead bees are washed in a colander under a flow of cold running water for the removal of honey and debris, and spread out on sheets of blotting-paper for superficial drying. The bodies are weighed and ground in a mortar to a thick paste, which is extracted with a moderate excess of Coca's fluid in the cold for 48 hours, with frequent stirring. The mass is squeezed through a clean, fine double-muslin bag, and the filtrate, collected and preserved with 0.5% phenol, is submitted to paper filtration followed by Seitz filtration. The clear straw-coloured fluid is controlled for sterility, and constitutes the "whole bee" extract.

Standardization of Whole-bee Extract

The "standardization" of the whole-bee extract is arbitrarily based on the total protein nitrogen content of the fluid. The figure thus obtained, and referred to as the "unitage," is taken as the basic "strength" of the particular batch of extract. It is of course no criterion of the allergenic value of the extract, and merely serves as a convenient guide to dilutions which may later have to be made.

Preliminary Skin-testing of the Patient

Skin-testing is regarded as a necessary preliminary to the desensitization process that is to follow. The object is to determine the degree of the patient's sensitivity in "units" to the particular batch of bee-protein extract in use. A "bee-venom skin-test outfit" is issued to physicians, consisting of a series of capillary tubes containing the whole-bee extract in the following graded strengths: 1, 10, 50, 100, 200, 500, 1,000, and 2,000 units per ml.

The skin tests are carried out as follows. With a tuberculin-type syringe, 0.02 ml. of the lowest-strength extract (1 unit) is injected into the skin of the volar surface of the forearm. Injections are continued in this way with the stronger extracts in the skin test outfit until the occurrence of a local reaction is just apparent—a weal about 1 cm. in diameter with a surrounding area of erythema. No further skin tests are done, but the "unitage" of the extract producing this reaction is noted. All test injections are given by the intracutaneous route in a fresh area of skin each time at intervals of 10 to 15 minutes to allow for the development of any reaction that might occur. In our experience, skin sensitivity is variously shown by sensitive patients to 1–250 units per ml. of fresh whole-bee extract.

A suitable treatment set for desensitization purposes is now prepared on the basis of the skin-test reaction.

Desensitization with Whole-bee Extract

Desensitization is carried out with injections of whole-bee extract by the *intracutaneous* route. This route is advised because the reactions are plainly visible and easily gauged, and dosage can accordingly be suitably regulated. Further, as the amount injected each time is relatively small there is a local reaction only, and, in our experience, no constitutional or other untoward reactions need be anticipated.

The treatment set provided for desensitization purposes consists of a series of dilutions of whole-bee extract of the same batch used for the skin testing in 2-ml. rubber-capped bottles in increasing strengths and commencing at a dilution somewhat less than the reaction-strength noted in the preliminary test.

The intracutaneous injections of each extract dilution are given in doses of 0.05–0.25 ml. at intervals of 2–4 days, with dose increments, when indicated, of 0.05 ml. It is desirable to obtain a weal 1–2 cm. in diameter after each injection. Increase of dosage or use of higher-strength extracts is indicated only when the weal reaction is beginning to diminish in size. It may happen that five, six, or more injections are given from the same extract before proceeding to higher strength.

Example: A positive reaction was obtained in the preliminary skin test with the 10-unit extract. The treatment set is prepared with a series of extracts containing 5, 10, 25, 50, 100, and 250 units per ml. When this course is completed a further series of stronger extracts from 250 units per ml. upwards is issued as indicated. It is desirable to continue desensitization with gradually increasing doses of extract until the patient is receiving injections of extracts of about 1,000 units strength with a local reaction only after each injection. When this final "unitage" of extract is readily tolerated, with the production only of a local weal of 1–2 cm. diameter, maintenance doses of 0.25 ml. each are injected thereafter at gradually increasing intervals until the patient is receiving such an injection once every three to four months. It has not been found necessary to use strengths of extracts higher than 2,000–3,000 units per ml. for effective desensitization. In highly sensitive persons—that is, those reacting to 1–10 units by skin test—it suffices to use a desensitizing extract not stronger than about 1,000 units (corresponding to 1,000–100 times the original skin reaction strength). This final

dosage is reached as a rule in 2–3 months. As in all "desensitization" procedures, it is inevitable that the state of hyposensitization attained will in due course be lowered if not lost. It is for this reason that maintenance doses as described should be continued for as long as thought necessary, especially in bee-keepers and others who cannot avoid contact with bees.

Results of Desensitization

A description has been given (Ordman, 1951) of three persons sensitive to bee stings in whom effective desensitization had been achieved with the use of whole-bee extract administered intracutaneously. Since that time 19 further instances of successful desensitization by this method have come to notice, bringing the total to 22. These 19 cases have emerged from a study of 47 satisfactorily completed reports by physicians who had submitted their bee-sting-sensitive patients to adequate desensitization. In 23 instances the patients had not been further stung by bees, and it is in the remaining 24, where stinging had followed desensitization, that these 19 persons were found to be fully protected (see Table).

It may seem surprising that only 22 authenticated instances of successful desensitization can be quoted when material for prophylactic desensitization had been supplied over the years for some hundreds of persons. The explanation is, firstly, that most people subjected to bee stings in South Africa live in the rural areas and information about them must be obtained by correspondence with their doctors, leading all too often to little or no details about their patients in spite of follow-up letters. Secondly, in the bulk of the replies that do become available the information is vouchsafed that, although the patients had been properly desensitized according to our instructions, they had not subsequently been stung by bees.

Details are given in the Table of the 24 cases which had been submitted to desensitization and about which full reports were obtained. Effects of bee stings before and after such desensitization, results of skin-sensitivity tests, and the desensitization procedure itself are described for each case.

It will be observed that in 19 of these cases (1–19) the results were highly satisfactory, as no reactions, or very mild reactions only, were now occurring in persons who were originally very severely affected by bee stings. In Case 20 "some improvement" only was claimed. In Cases 21, 22, 23, and 24 it was reported that desensitization procedures had produced no benefit at all—that is, reactions after bee stings were now as severe as they had been previously.

Cases 21, 22, 23.—These patients were highly sensitive by skin test to whole-bee extract (10 units). Desensitization was carried out to only 100 units or less instead of to the required 3,000–4,000 units. Desensitization in each of these cases was obviously inadequate, and satisfactory results could not be expected.

Case 24.—For some reason this patient does not appear to have been highly skin-sensitive to whole-bee extract (1,000 units) by test, and desensitization should have gone on with strengths up to 4,000 units or even higher.

It becomes clear from the study of the Table that desensitization with whole-bee extract by the intracutaneous method is a very satisfactory procedure if properly carried out.

Summary and Conclusions

A procedure is described for the prophylactic desensitization of persons sensitive to bee stings by the use of increasing strengths of whole-bee extract administered intracutaneously.

A preliminary intracutaneous skin test is performed to determine the degree of the patient's sensitivity to the extract that is to be used for subsequent desensitization.

Successful desensitization is reported of 19 persons originally highly sensitive to bee stings.

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THE POLYSACCHARIDE BEHAVIOUR OF CANCER ANTIGENS

BY

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The high degree of accuracy in the detection of antigens in the sera of patients with carcinoma obtained by use of the Schultz–Dale method has already been reported (Makari, 1955a, 1955b). Recently Burrows (1958) confirmed these results in a thorough investigation of the test. The chemical nature of cancer antigens remains an unsolved problem. However, in studying host–tumour relationships it is extremely important to know the exact nature of these cancer antigens. In an effort to elucidate this problem, Burrows and Neill (1958) have investigated the nature of the immunologically active constituent of serum of patients with carcinoma. They attribute the antigenic activity of such sera in the Schultz–Dale test to the presence of a polypeptide.

The following application of the Schultz–Dale method leads us to believe that cancer antigens behave like polysaccharides and that the activity observed by Burrows and Neill in the polypeptide of the serum is probably due to an associated polysaccharide antigen.

Methods

Details of the Schultz–Dale method, the preparation of antigens, and the testing procedure have been described (Makari, 1955b). Tumour and normal tissues are homogenized in 0.2N saline solution (one part of tissue plus four parts of saline) with a Sorvell homogenizer immersed in cracked ice. This procedure is allowed to continue for 10 minutes with the rheostat set at 115. The homogenate is then centrifuged twice at 3,000 r.p.m. at 5° C. for 10 minutes. The sediment is discarded and the supernatant is further centrifuged for 30 minutes at 10,000 r.p.m. at the same temperature. This sediment is separated and resuspended up to volume with normal saline solution. It is to be noted that this sediment differs from that used in my earlier work (Makari, 1955a, 1955b) in that the latter was obtained between 3,200 and 4,000 r.p.m. The sediment used in the present study—that is, that obtained between 3,000 and 10,000 r.p.m.—was chosen because it was found to have antigens in common with various tumours (Makari, 1958a).

The resuspended sediment and its supernatant comprise the antigens used in this study. They are used both in this form and after treatment by a procedure described by Chang (1953) and Chang, Snyder, and Murray (1953) in their preparation of an erythrocyte-sensitizing substance from rickettsial antigen which was thought to be polysaccharide in nature. In this procedure an equal volume of ether is added, with vigorous shaking for five minutes. It is then left undisturbed, to allow separation into ether and aqueous phases. The aqueous phase is mixed with alkali in the following proportion: nine volumes of the aqueous phase to one volume of 2N NaOH. The mixture is kept in a water-bath at 100° C. for 30 minutes. It is cooled and dialysed for two hours at 0 to 4° C. against several changes of isotonic phosphate saline solution (Na_2HPO_4, 0.81 g.; KH_2PO_4, 1.04 g.; NaCl, 6.8 g.; distilled H_2O, 1,000 ml.; pH=6.8). The active material found inside the dialysis bag is then shaken with an equal volume of chloroform for 20 minutes and centrifuged at 2,000 r.p.m. for 15 minutes. In this study the chloroform layer is discarded and the clear aqueous phase containing the sensitizing substances (which are referred to as S.S.) is used. These behave as polysaccharides, being non-dialysable, resistant to boiling and alkalis, and giving a positive Molisch test.

In an effort further to evaluate the polysaccharide nature of cancer antigens another method was used which is very similar to that described for the preparation of pneumococcal polysaccharides (Whistler and Smart, 1953).

In this method, melanoma antigen (fraction O), in equal amounts, is added to 95% ethanol chilled at 0° C. This is centrifuged and the supernatant discarded. The sediment is suspended in 80 ml. of acetate buffer (157.5 g. of $NaC_2H_3O_2.3H_2O$ in three litres of distilled water and the *p*H adjusted to 6.05 with glacial acetic acid). This is then ground slowly at 0° C. and centrifuged.

From the supernatant, the polysaccharide (fraction A) is precipitated by the addition of 5 volumes of cold isopropyl alcohol. The residue from the first grinding is again suspended in 80 ml. of acetate buffer and ground at 0° C. The suspension is centrifuged and the supernatant precipitated with isopropyl alcohol (fraction B).

Fraction A is removed by centrifugation and dissolved in 100 ml. of cold distilled water. The resulting turbid greenish solution is deproteinized by the Sevag method in which 50 ml. of chloroform is added in 10 ml. of butyl alcohol for each 150 ml. of solution, and agitated from time to time in a homogenizer at 3° C.

The resulting emulsion is centrifuged, and the aqueous layer containing polysaccharide is separated. The aqueous layer is then adjusted to a concentration of 3% sodium acetate with saturated sodium acetate solution brought to *p*H 6 with acetic acid.

One half-volume of cold isopropyl alcohol is added to precipitate the polysaccharide, and the suspension is left overnight. The Sevag procedure is repeated until the material is completely deproteinized, after which the polysaccharide is centrifuged. This polysaccharide-like substance is referred to as P.L.S.

TABLE I.—*Parallel Behaviour by the Schultz–Dale Method, of Guinea-pig Uterine Horns Immunized Against Tissue Antigens and Their Corresponding Polysaccharide S.S.*

Reaction No.	Reaction Released By: Type	Amount	Guinea-pigs Immunized With S.S.: Normal Colon, Handy-Ag.194-S.S.	Ca. Colon, Handy-Ag.195-S.S.	Reaction No.	Releasing Antigen: Type	Amount	Guinea-pigs Immunized With Antigen: Normal Colon, Handy-Ag.194	Ca. Colon, Handy-Ag.195
(A) 1	Normal serum (10 additions)	0·3 ml.	(2) 1	(15) 1	(B) 1	Normal colon, Handy-Ag.194	0·1 ml.	0	(6) 1*
11	" " 3 "	0·3 "	0	(5) 1	2	" " "	0·1 "	0	(3) 2*
14	" "	0·1 "	0	(3) 1	3	" " "	0·1 "	0	(2) 2
15	Ca. vulva. Oliver serum (18053)	0·1 "	0	(10) 1*	4	Normal colon, Handy-supernatant after 10,000 r.p.m. (9 additions)	0·1 "	(20) 1*	(10) 1*
16	Normal serum	0·1 "	0	0					
17	Ca. lung. Brunson serum 18077	0·1 "	0	(6) 1	13	" " "	0·1 "	0	0
18	Normal serum	0·3 "	0	0	14	Normal colon, Handy-Ag.194	0·3 "	0	0
19	Ca. vulva. Oliver serum (18053)	0·3 "	0	0	15	" " " (ether extracted)	0·3 "	(2) 1*	(7) 1*
20	Normal serum S.S.	0·3 "	0	0					
21	Histamine	10 μg.	(7) 1*	(15) 1*	16	Ca. colon, Handy-Ag.195	0·3 "	0	0
					17	" " (ether extracted)	0·3 "	0	(5) 1
					18	Handy-Ag195 (supernatant)	0·2 "	0	(8) 1
					19	Briggs-S.S. Fibrosarcoma	0·2 "	0	(7) 1
					20	Ca. breast, S.S.	0·2 "	0	0
					21	Histamine	10 μg.	(15) 1*	(12) 1*

Figures in parentheses represent the height of uterine contractions in mm. Figures 1 and 2 outside parentheses refer to the reaction taking place at the first or second half of the tracing. The asterisk designates a strong maintained reaction.

TABLE II.—*Behaviour of Homologous and Autologous Tissue Antigens and Their Polysaccharide S.S. by the Schultz–Dale Method*

Reaction No.	Reaction Released by: Type	Amount	Guinea-pigs Immunized with S.S.: Normal Colon, Handy-Ag.194 S.S.	Ca. Colon, Handy-Ag.195 S.S.	Reaction No.	Reaction Released by: Type	Amount	Guinea-pigs Immunized with Antigen: Normal Kidney, Ag.128	Acute Leukaemic Kidney, Ag.208
(A) 1	Normal serum donor	0·2 ml.	0	(2) 1	(B) 1	Normal plasma	0·5 ml.	(18) 1*	(27) 1*
2	" " "	0·2 "	0	(1) 1	2	" " "	0·5 "	(13) 1	(22) 1*
3	Ca. stomach (18385)	0·2 "	(1) 1	(5) 1*	3	" " "	0·5 "	0	(22) 1
4	Ca. breast (18537)	0·2 "	0	(18) 1*	to 6	" " "	0·5 "		0
5	Normal serum donor	0·2 "	0	(2) 1	7	Normal kidney, Ag.128	0·1 "	0	(18) 1
6	Ca. lung (18245)	0·2 "	(24) 1*	(16) 2*	8	Normal serum	0·3 "	0	0
7	Normal serum donor	0·2 "	(2) 1	(5) 1	9	Hodgkins (18386)	0·3 "	0	(15) 2*
8	Melanoma (18370)	0·2 "	(18) 2*	(20) 1*	10	Normal serum	0·3 "	0	0
9	Normal serum donor	0·2 "	0	(5) 1	11	Carcinoma (18248)	0·3 "	0	(31) 1*
10	Histamine	10 μg.	(26) 1*	(20) 1*	12	Histamine	10 μg.	(25) 1*	(31) 1*

Reaction	Reaction Released by: Type	Amount	Guinea-pigs Immunized with Antigens: Normal Colon, Handy-Ag.194	Ca. Colon, Handy-Ag.195	Reaction	Reaction Released by: Type	Amount	Guinea-pigs Immunized with Ether Extracted Antigens: Normal Colon, Handy-Ag.194E	Ca. Colon, Handy-Ag.195E
(C) 1	Normal colon, Handy-Ag.194	0·1 ml.	(10) 1*	(18) 1*	(D) 1	S.S. normal donor	0·5 ml.	(14) 1	(4) 1
2	" " "	0·1 "	0	0	10	" " "	0·1 "	(10) 1*	(3) 1
3	Ca. colon, Handy-Ag.195	0·1 "	(1) 1*	(11) 1*	11	Normal donor serum	0·3 "	(13) 1*	(15) 1*
4	Normal colon, Handy-Ag.194	0·1 "	0	0	12	" " "	0·3 "	(5) 1	0
5	" " Handy-Ag.194-SS	0·05 "	(2) 1	(8) 1	13	S.S. ca. colon, Handy-Ag.195-SS	0·05 "	(1) 2	(10) 1*
6	Ca. colon, Handy-Ag.195.SS	0·05 "	0	0	14	Histamine	10 μg.	(14) 1*	(15) 1*
			(23) 1*	(21) 1*					
7	Histamine	10 μg.	(23) 1*	(21) 1*					

Immunization of guinea-pigs is passive with rabbit antiserum (I.V.) in Section A, and is active in others.

Virgin female guinea-pigs are immunized, by the help of Freund's adjuvants, either with S.S. or with the original antigens obtained from neoplastic tissues. Control antigens and their corresponding S.S. are prepared from "normal" sections of the same organ from which the cancer tissue is obtained, and also from similar organs of a young healthy adult.

In three to four weeks the guinea-pigs are sacrificed and their uterine horns are used in a Schultz–Dale bath. Rabbits similarly immunized are bled and their sera used for passive *in vitro* or *in vivo* (intravenous) sensitization. To release the local *in vitro* anaphylactic reaction of the uterine muscle, various tissue antigens, their S.S. and P.L.S., are used, as well as sera from normal blood donors and from patients with cancer.

These reactions are recorded in mm. in Tables I and II. In Table III results are shown in terms of contraction index (C.I.). This is the ratio of the specific contraction in mm. to that resulting from 10 μg. of histamine base.

TABLE III.—*Immunological Activity by the Schultz–Dale Method of a Polysaccharide-like Substance (P.L.S.) and Its Two Fractions A and B Prepared from Melanoma Antigen. (Results are Recorded in Terms of Contraction Index (C.I.). 0.1 ml. was Used to Release the Reaction)*

Reaction No.	Reaction Released by	Pigs Immunized with Melanoma Ag., Sed. IIIB (3,000–10,000 r.p.m.)	
		Horn A	Horn B
1	Normal serum	0	0
2	Normal Ag.	0	0
3	Melanoma Ag. Sed. IIIB *Fraction O*	(0·10) 2 *	(0·12) 2*
4	Melanoma Ag.	(1·0) 1*	(0·87) 1*
5	Sed. IIIB	(0·73) 1*	(0·87) 1*
6	*Fraction A*		
7	Melanoma Ag. Sed. IIIB *Fraction B*	(0·25) 2*	(0·36) 2*
8	Melanoma Ag. Supernatant 10,000 r.p.m.	(0·87) 2*	(0·91) 2*
9	Histamine (10 r)	(1·0) 1*	(1·0) 1*

Results

In general, the same result is obtained from guinea-pigs immunized with both S.S. and the original antigens. Furthermore, S.S., P.L.S., and original antigens release the Schultz–Dale reactions equally well.

In fact, the polysaccharide-like fractions, A and B, give a higher contraction index than does the original melanoma antigen (fraction O), fraction A giving the highest figures (see Table III). Desensitization is possible with these reactions.

Some typical reactions are shown in Tables I and II. After desensitization to normal serum and normal tissue antigens, the uterine horns from the cancer-immunized guinea-pigs still react positively in response to sera or tissue antigens from carcinoma or related tumours. Table I shows this phenomenon clearly. Thus, in Table I,A the uterine horns of guinea-pigs immunized to S.S. carcinoma of the colon (Ag.-SS.195 (Handy)) reacted specifically (after desensitization to normal serum in reactions A1 to A14) with sera from carcinoma patients (reactions A15 and A17), but not with sera from normal donors (reactions A16 and A18). On the other hand, control uterine horns of guinea-pigs immunized to S.S. "normal" colon (Ag.-SS.194 (Handy)) did not react to these same sera from carcinoma patients or from normal donors (after desensitization to normal serum).

The immunological specificity of these positive reactions is strongly suggested by desensitization procedures in which the sensitized uterine horns initially exposed to a positive reacting serum or a tissue antigen fail to react to the same antigen after these horns are washed and exposed again. This indicates specific neutralization of antibodies fixed to the horn by their specific antigens and excludes the possibility of a non-specific pressor effect. For example, Table I shows a marked reaction to serum from carcinoma case 18053 in A15; a weaker reaction to serum from another carcinoma, 18077, in A17; and no reaction at all on second contact with carcinoma serum, 18053, in A19.

Table I,B shows a similar behaviour of the uterine muscles from guinea-pigs immunized to the native original antigens —that is, carcinoma of the colon (Ag.195 (Handy)) and "normal" colon (Ag.194 (Handy)), as was shown for their S.S. counterpart. In addition, the comparative strength of various antigens in releasing the reaction is shown. Ether extraction of antigens 194 and 195, for example, improved their antigenicity, as shown by their ability to release the reaction in the Schultz–Dale bath (Table I,B, 14, 15, 16, and 17). Furthermore, the capacity of these antigens to immunize guinea-pigs was well preserved even after their ether extraction (Table II,D). It is also apparent that after centrifuging at 10,000 r.p.m. the supernatant fraction of the antigen is much more effective in releasing the reaction than the sediment even when the latter is ether extracted (see Table I,B: 3, 4, 16, 17, and 18).

Table II further reveals the parallel behaviour of S.S. and of original antigen. It also shows the behaviour of autologous antigens (wherein neoplastic and "normal" tissues are taken from the same patient) as compared with homologous antigens (wherein the neoplastic and the control normal tissues are taken from a carcinoma patient and from a healthy accident victim respectively). In the case of autologous antigens the so-called "normal" tissue is not altogether normal immunologically. Although it shows mostly normal tissue components for the most part when the full antigen is used for immunization of guinea-pigs (Table II,C, 1 and 5; D, 1 to 12), it does show carcinoma components when S.S. is used for immunization (Table II,A, 6 and 8) and for releasing the reaction (Table II,C, 5 and 6). In the latter case both "normal" colon (Ag.194-S.S. (Handy)) and carcinoma of the colon (Ag.195-S.S. (Handy)) possess the same abnormal components although they are present to a lesser degree in the "normal" tissue. Furthermore, desensitization indicates that these abnormal components are antigenically similar to the carcinoma antigen. Thus we see that prior addition of "normal" colon (Ag.194-S.S. (Handy)) to the carcinoma horn (Table II,C, 5) desensitized it completely to further addition of carcinoma of the colon (Ag.195-S.S. (Handy)). However, the same amount of Ag.195-S.S. did react specifically with another similarly sensitized horn (Table II,D, 13). This was not the case, however, when autologous tissue antigens were used from a healthy person. This is shown by Table II,B, in which tissue antigens are prepared from the kidney of a patient with acute leukaemia and control antigens are prepared from the kidney of a young victim of a car accident. Only normal tissue antigens were found in the healthy kidney.

The common antigenicity between various types of malignant tumours is shown in Table I,A, 15 and 17; between fibrosarcoma and carcinoma in Table I,B, 19 and 20; between various types of carcinomas and melanomas in Table II,A, 3, 4, 6, and 8; and between leukaemia, Hodgkin's disease, and carcinoma in Table II,B, 9 and 10. This aspect will be studied in other articles (Makari, 1958a, 1958b).

Discussion

The immunologically active substances in the serum and tissues of cancer patients behave like polysaccharides when studied by the Schultz–Dale test. They are precipitated by isopropyl alcohol, and their activity is maintained, and even improved, after deproteinization with chloroform and butyl alcohol. Burrows and Neill (1958) showed that acid hydrolysis resulted in complete loss of activity. This does not contradict the polysaccharide nature of these antigens, since acid hydrolysis of polysaccharides is known to destroy their antigenicity. Extraction with 2N NaOH, however, hydrolyses

the bonds between carbohydrates and proteins (Meyer and Rapport, 1951), while heat to 100° C. denatures the proteins. This probably explains why treatment with heat and alkalis does not destroy their ability to immunize guinea-pigs or to release the Schultz–Dale reaction. The fact that such activity persists after ether extraction tends to refute the lipid nature of cancer antigens. The slight improvement in antigenicity resulting from ether extraction is again consistent with a polysaccharide nature, since polysaccharides have a great affinity for lipids.

Moreover, the polysaccharide nature of the antigen explains the greater activity of the supernatant, as compared with the sediment, in releasing the Schultz–Dale reaction. The less soluble and less active components are probably the result of gradual drying of tissues. This, according to Whistler and Smart (1953), occurs when highly hydrated polysaccharide material is air-dried. The gradual removal of water molecules allows neighbouring polysaccharide molecules to come together and establish strong bonds which later restrain the separation of molecules. This reduction in surface area and in the number of active available sites on the polysaccharide molecules could be regarded as a form of polymerization, and would account for the *in vitro* reduction of antigenic activity—that is, its capacity to release the reaction in the Schultz–Dale bath—of the sediment as compared with the supernatant.

These studies also raise the question of the relatively "normal" nature of the healthy colon tissue obtained from the patient Handy, who did have a carcinoma of the colon. Is pathologically "normal" tissue necessarily immunologically "normal"? Is the better control tissue to use in this case "normal" colon from the same patient or from a young healthy accident case?

The above findings indicate the presence of the specific carcinoma polysaccharide-like antigens in these so-called "normal" portions from the carcinoma patients, although to a less extent than in the neighbouring neoplastic tissue. They also indicate that this soluble polysaccharide-like antigen is present not only in the cancerous tissue but also in the blood and other tissues, even those that appear pathologically "normal." This was the reason for the use in later studies of homologous tissues from a healthy individual rather than from the cancer patient himself.

The polysaccharide nature of cancer antigens could easily explain why mast cells and tissue polysaccharides are the predominating elements in the development and growth of connective-tissue tumours as shown by Sylvén (1945), Holmgren and Wohlfart (1947), and Gersh and Catchpole (1949). It could also explain the greatly increased amounts of polysaccharides always found in the serum of cancer patients. Furthermore, it throws new light on the finding of high levels of hyaluronidase inhibitors in the blood of patients with disseminated cancer by Kiriluk *et al.* (1950) and with certain leukaemias and lymphomas by Hentstell and Freedman (1951).

The association of polysaccharides with polypeptides is well known. Morgan (1941) and Partridge and Morgan (1942), for example, were able to make artificial complexes using "polypeptide-like" substances isolated from Shiga, and carbohydrates such as group A substance from commercial pepsin. It was found that these "polypeptide-like" substances appear to have a special power to form antigenic complexes with polysaccharides.

It is our belief that the activity of the polypeptide found by Burrows and Neill (1958) in the serum of cancer patients is due to an associated polysaccharide antigen. The finding by Winzler (1953), referred to by Burrows and Neill, of an increase in polypeptides in the serum in carcinoma, and specifically of mucopolypeptides, strengthens this possibility.

Polysaccharides are less complex to study immunochemically than are proteins. This finding, therefore, of the polysaccharide nature of cancer antigens should give us a little more reason for optimism in our attempts to understand the cancer problem and a greater hope of its solution.

These results are preliminary in nature, and work along these lines is being continued at the Muhlenberg Hospital. Further evidence for the polysaccharide nature of cancer antigens, using another immunological technique, will be published elsewhere.

Summary

Substances distinctly polysaccharide-like in nature have been prepared from cancer and normal tissue antigens by two procedures: (1) by precipitation with isopropyl alcohol and deproteinization with chloroform and butyl alcohol (P.L.S.); and (2) by heat and alkali treatment (S.S.).

The specific immunological activity of cancer antigens seems to reside in these polysaccharide-like substances.

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DETECTION OF ANTIGENS IN SERA OF PATIENTS WITH NEOPLASTIC DISEASE BY SCHULTZ–DALE TEST

ITS POSSIBLE USE AS A SCREENING PROCEDURE FOR TUMOURS

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In search of a specific diagnostic serological test in cancer we have looked for a high degree of positive results in known cancer cases and a high degree of negative results in non-cancerous disease. Dunn and Greenhouse (1951) tentatively set limits of 90% accuracy in cases of cancer and 95% accuracy for patients with non-cancerous disease.

Makari (1955) described the use of the Schultz–Dale test for the detection of carcinoma antigen in the serum of patients with carcinoma. It was shown that, when the carcinoma antigen used for immunization of guinea-pigs was the sediment obtained between 3,200 and 4,000 r.p.m., this test would conform to the criteria set up by Dunn and Greenhouse—that is, it was positive in 96.8% of proved carcinoma cases and negative in 95.2% of non-cancerous lesions.

Recently Burrows (1958) was able to confirm our results in a large series of 508 patients, and recorded an accuracy of 96.7% in proved carcinoma cases and of 96.7% in non-cancerous lesions. This establishes the

use of such a procedure as a *diagnostic* test, but the need still remains for a *screening* test which would detect not only carcinomas but other tumours as well. Such a screening test, however, should not be subject to some of the criteria established by Dunn and Greenhouse for a diagnostic test—for example, the requirement that there be not more than 5% of "false-positive tests" (a test which is positive, although the patient does not have a clinically apparent cancer). The principal aim of such a screening test would be the detection of tumours in this preclinical stage. In fact, a good screening test should show more of these so-called "false positives," and, to be a practical test, it should detect not only carcinomas but all tumours.

Working on the hypothesis that the change from a state of carcinogenesis to pre-tumour, tumour, and tumour differentiation is associated with a gradual increase in the size of the antigenic particles (as these particles become incorporated with certain components of the host), and that such a change is accompanied by an increase in specificity, one would expect that, by using antigenic particles smaller than those used in our previous work, components which are less group-specific and which have a wider antigenic spectrum would be found.

In fact, by the use of carcinogens as immunizing antigens to guinea-pigs, it should ultimately be possible to reach the lowest common denominator of all tumours, and to detect in the serum of patients carcinogen-like substances in the early stage of carcinogenesis before clinical cancer develops. In this and in another paper, evidence is presented in support of this hypothesis. The purpose here is to show that, by using for immunization of guinea-pigs antigens with smaller particles than those I previously used, it is possible to detect antigenic components in the serum which are common to patients with various types of neoplastic disease, and to show that such a procedure might be utilized as a screening test for tumours.

Some aspects of immunological relationships between various tumours are also referred to.

Method

The technique employed is essentially the same as that used by Makari (1955), except that an antigenic fraction with smaller particles is used for immunization of guinea-pigs.

A 20% aqueous emulsion of a tumour is made in 0.2N saline solution. The sediment II previously used was obtained by centrifugation at 3,200 r.p.m., equivalent to an R.C.F. of 1.5 kg./g., and recentrifugation at 4,000 r.p.m., equivalent to an R.C.F. of 2.3 kg./g. Sediment III (also used before) was obtained by centrifugation between 4,000 and 10,000 r.p.m., equivalent to an R.C.F. of 10.3 kg./g. In this study a modified sediment III, to be referred to as sediment IIIB, is used. This is the sediment obtained by centrifugation at 3,000 r.p.m., discarding the sediment, and recentrifugation at 10,000 r.p.m.—that is, between 3,000 and 10,000 r.p.m. This sediment (IIIB) is suspended in normal saline solution (to original volume) and is injected subcutaneously with Freund's adjuvants into young virgin female guinea-pigs. These guinea-pigs are sacrificed after one month and used in a Schultz–Dale bath. For passive sensitization, rabbits are similarly immunized but are given a second dose two weeks later. This is followed by a third dose a week afterwards. They are bled 7 to 10 days after the last injection. The rabbit antisera are adsorbed with guinea-pig kidney (to remove Forssman antibody) and are then either injected intravenously or diluted (1 part to 250) with Tyrode's solution, and allowed to come in contact with a uterine horn from a non-immunized guinea-pig for one hour at 5° C. and with air bubbled into the mixture.

Carcinomas of varying types were used for immunization of guinea-pigs. These were carcinomas of the breast, rectum, colon, and stomach, and squamous carcinomas of lung and oesophagus. Other tumours were also used: fibrosarcoma, melanoma, acute leukaemia, and lymphoma.

One further modification was introduced for the evaluation of these reactions. For a test to be regarded as a true positive, evidence of desensitization was required—that is, it should be possible to obtain decreasing reactions or no reactions at all to the same serum when the uterine horn is washed and re-exposed to it at the same dose level. Those cases which did not fulfil this criterion were included with the questionable group. Uterine horns not adequately sensitized and not reacting with a known positive serum were discarded. Sera added to the horn at the end of the run and not followed by a known positive reaction could not be evaluated and are not included in this series.

For certain studies of antigenic relationships between tumours, two experiments are reported. In one, segments from the ileum of one guinea-pig were used instead of the uterine horns, and Tyrode's solution with full-strength calcium was used instead of the half-strength we use with uterine horns. Passive sensitization *in vitro* was done with antisera from rabbits immunized with various types of tumours. The reactions were triggered by the addition of supernatants—that is, where sediment at 10,000 r.p.m. was removed. In another study the uterine horns from guinea-pig 415 actively immunized against carcinoma of the colon (antigen 70) were used. The two horns from the same guinea-pig were divided into four segments, which were used in separate baths. To release the reactions, various dilutions of carcinoma and sarcoma supernatants were used, one horn receiving carcinoma supernatant, another carcinoma sediment, the third sarcoma supernatant, and the fourth sarcoma sediment. Each horn was then completely desensitized to the antigen added to it, and the releasing antigens were reversed so that sarcoma was added to the horn receiving carcinoma, and vice versa. This experiment was carried out in collaboration with Dr. P. Krag, of the State Serum Institute in Copenhagen, while he was visiting our laboratories.

Results

By the use of a modified Schultz–Dale test for tumour screening—that is, where *carcinoma* sediment IIIB (between 3,000 and 10,000 r.p.m.) was used as immunizing antigen—the following positive results were obtained in 444 individuals (Table I): 90.2% of 215 proved carcinomas; 62.0% of 55 proved malignant tumours other than carcinoma; 94.2% of 35 patients with benign tumours; 77.9% of 59 suspected tumours and early pre-cancerous lesions; and 12.5% of 80 blood donors. Similarly, of 704 normal serum specimens from the blood bank (other than the 80 donors reported earlier), 12.6% were positive.

TABLE I.—*Schultz-Dale Reactions in* 444 *Individuals and in* 704 *Normal Serum Specimens Using a Modified Test for Tumour Screening with Carcinoma Sediment IIIB as the Immunizing Antigen for Guinea-pigs*

Cases Studied	Result of Test			Total
	Negative	Question-able	Positive	
Carcinoma	8 (3·7%)	13 (6·1%)	194 (90·2%)	215
Other malignant tumours	12 (21·8%)	9 (16·2%)	34 (62·0%)	55
Benign tumours	2 (5·8%)	0 (0%)	33 (94·2%)	35
Suspected cancer cases referred to tumour institute, and precancerous lesions	9 (15·2%)	4 (6·9%)	46 (77·9%)	59
Healthy donors	60 (75%)	10 (12·5%)	10 (12·5%)	80
Normal serum specimens from blood bank (other than those above)	568 (80·6%)	37 (6·8%)	99 (12·6%)	704

When *fibrosarcoma* sediment IIIB (between 3,000 and 10,000 r.p.m.) was used as the immunizing antigen the following positive results were obtained in 61 cases: 88% of

TABLE II.—*Results in 122 Cases of Proved Cancer*

Cases Studied	Antigen Used for Immunization of Guinea-pigs for Schultz–Dale Test							
	Fibrosarcoma Sediment IIIB		Melanoma Sediment IIIB (Amelanotic)		Melanoma 158 Sediment IIIB (Melanotic)		Melanoma 80 Sediment (Melanotic) IIIB	
	Positive	Total	Positive	Total	Positive	Total	Positive	Total
Malignant melanoma	6 (75%)	8	12 (75%)	16	6 (86%)	7	13 (87%)	15
Carcinoma	28 (85%)	33	8 (80%)	10	1	3	0	1
Breast	2	2	1	1				
Cervix	1	3						
Oesophagus	1	1	2	4				
Larynx	1	1	1	1				
Pancreas	1	1						
Parotid	0	1						
Pharynx	1	2						
Prostate	4	5						
Rectum	1	1					0	
Skin	1	1	2	2	1	3	0	1
Stomach	6	6	1	1				
Tongue	2	2						
? Origin	7	7	1	1				
Sarcoma	15 (88%)	17	4 (80%)	5				
Fibrosarcoma	9	9	2	3				
Lymphosarcoma	2	3	2	2				
Osteogenesis sarcoma	4	5						
Lymphoma–Leukaemia	2 (66%)	3	2 (50%)	4				
Leukaemia			2	3				
Lymphoma	2	2						
Hodgkin's	0	1	0	1				
Total	51 (83·6%)	61	26 (74·3%)	35	7 (70%)	10	13 (81·3%)	16

TABLE III.—*Antigenicity of Tumours as Shown by the Schultz–Dale Test*

Releasing Antigens† (Supernatant) Used	Antibodies Fixed to Ileal Segments from Rabbit Antisera Diluted to 1 250 Against								
	Ca. Lung (Ag.87) Rab. 417	Ca. Parotid (Ag.140) Pool 15	Lymph. Mel. (Ag.152) Pool 10	Ca. Breast (Ag.176) Pool 17	F.S. (Ag.14) Rab. 410	L.S. (Ag.165) Pool 11	Lymph. (Ag.81) Rab. 412	Ca. Liver (Breast) Ag.51 Pool 8	Mean Cont. Index for Supernatant
F.S. ? Ag.217	0	0	0	0	0	0	(0·08) 2	0	0·01
Adenocar. liver from rectum Ag.203	0	0	0	0	(0·08) 1	0	(0·20) 1*	(0·28) 2*	0·070
L.S. Ag. '65	0	(0·08) 1	0	(0·08) 1*	(0·11) 1	(0·16) 2	(0·16) 1	0	0·072
Mel. Ag.192	0	0	0	0	(0·18) 1	(0·06) 1	(0·20) 1*	(0·23) 2	0·08
Mel. Ag.152	(0·16) 1	(0·11) 1	(0·30) 1	(0·08) 1*	0	(0·22) 1	0	(0·41) 1	0·16
Ca. oesoph. Ag.220	(0·16) 1*	(0·20) 1*	(0·30) 1*	(0·44) 1*	(0·40) 1*	(0·37) 1*	(0·80) 1*	(0·90) 1*	0·44
	0	0	0	0	0	0	0	0	
Ca. lung Ag. 233	(0·22) 1*	(0·32) 1*	(0·35) 1*	(0·60) 1*	(0·36) 1*	(0·56) 1*	(1·04)	(1·14) 1*	0·57
	0	0	0	0	0	0	(0·70)	(1·0) 1*	
Mean C.I.–Sed.	0·08	0·10	0·13	0·17	0·18	0·196	0·34	0·42	

Antigens for rabbits with the exception of Ag.51 are made up of sediment III B. Ag.51 has in addition sediment at 3,000 r.p.m. included. Figures in parentheses represent contraction indices (ratio of specific contraction to histamine contraction). Figures 1 and 2 outside parentheses indicate whether contraction occurred in the first or second half of the run. * Strong maintained reaction. † Desensitization with normal serum and normal tissue antigens was done before the addition of cancer antigens, but is not reported in this table.

17 sarcomas, 85% of 33 carcinomas, and 75% of 8 melanomas. Two cases of lymphoma were positive, but one case of Hodgkin's disease was negative (see Table II). When three *melanoma* sediments IIIB (between 3,000 and 10,000 r.p.m.) were similarly used as immunizing antigens, the following results were obtained in 61 cases: 75% of 16 cases of melanoma were positive with the amelanotic Ag., 86% of 7 cases of melanoma with melanotic Ag.158, and 87% of 15 cases of melanoma with melanotic Ag.80. Eight out of 10 cases of carcinoma were positive and four out of five cases of sarcoma were positive. Two out of three cases of leukaemia were positive, but one case of Hodgkin's disease was negative. In other studies Hodgkin's disease was shown to have common antigenicity with leukaemia. The overall percentages of positive reactions were as follows: 89% of 262 carcinomas, 73% of 130 malignant tumours other than carcinomas, 94.2% of 35 benign tumours, 77.9% of 59 cases with pre-cancerous lesions and suspected tumours, 12.5% of 80 healthy donors, and 12.6% of 704 serum specimens from the blood bank.

Some studies on antigenic relationships among tumours are shown in Tables III and IV. The results indicate a spectrum of common antigenicity which is narrowest in carcinoma of the breast and widest in lymphoma (see Table III). Results of the second experiment (shown in Table IV) demonstrate some antigenic relationships between carcinoma of the colon and sarcoma. It was found that the supernatants gave a reaction in a higher dilution than the sediment. Furthermore, desensitization was easier to perform with the sediment than with the supernatant. Desensitization to carcinoma reaction prevented the appearance of a sarcoma reaction, while desensitization to sarcoma allowed the later appearance of a carcinoma reaction.

TABLE IV.—*Cumulative Additions of Increasing Concentrations of Antigen 61 to Segments of Horns from Guinea-pig 415 Sensitized Actively to Carcinoma of Colon (Ag.70)*

Reaction Released by 1 ml. Dilutions	Ca. Supernatant (10,000 r.p.m.)	Sa. Supernatant (10,000 r.p.m.)	Ca. Sed. IIIB	Sa. Sed. IIIB
1 64	0	(6) 1	0	0
+1 32	(7) 1	(9) 1	0	0
+1 16	(10) 1	(12) 1	0	0
+1 8	(43) 1*	(17) 1	0	0
+1 4		(26) 1*	(10) 1	(46) 2*
+1 2			(58) 1*	(8)*
1 2	0	(5) 1	(2) 2	0
	Sa. Supt.	Ca. Supt.	Sa. Sed.	Ca. Sed.
1 2	0	(32) 1*	0	(49) 1*
1 2		(12) 1		0
Histamine (10r.)	(47) 1*	(34) 1*	(59) 1*	(51) 1*

Complete desensitization to normal serum and normal tissue antigens was done before addition of cancer antigens. Figures in parentheses indicate height of contraction of uterine horn. Figures 1 and 2 outside parentheses indicate time of contraction whether in the first or second half of the run. Asterisk indicates a strong maintained contraction.

Discussion

It is apparent that by the proper choice of the immunizing antigen one can utilize the Schultz–Dale test both as a type-specific *diagnostic serological test for carcinoma*, or also, as shown in these studies, as a *serological screening*

test for all kinds of tumours. The finding that benign tumours and pre-cancerous lesions (such as hyperkeratosis, hyperplasias, etc.) give as high a percentage as malignant tumours indicates the further usefulness of this procedure as an early screening test for tumours.

A negative test would mean that the presence of a tumour is unlikely, while a positive test is a signal indicating the presence of a benign or malignant growth, or even a pre-cancerous lesion which should be further investigated. Therefore the significance of such a test from the point of view of early detection is much greater than the test we described earlier, but is less useful for establishing a definite diagnosis. It is of interest to note that malignant tumours other than carcinoma gave fewer positive results than benign tumours, including even early hyperplasias or suspected tumours. This finding by itself suggests the usefulness of such a test for early detection of tumours and for screening purposes.

It is of interest to note that, although this screening procedure detects common antigens in various tumours, it still detects its own type of tumour to a greater extent—that is, type-specificity is not completely lost. Thus when sarcoma sediment IIIB is used, the highest percentage of positives (88%) is still in sarcomas as compared with carcinomas and melanomas. When melanoma sediment IIIB is used (from melanoma 158 and 80), 86% and 87% positive results are obtained with melanomas. The persistence of type specificity is due in part to the inclusion of cancer-specific antigens sedimented at 3,200 to 4,000 r.p.m.—that is, sediment II—in the 3,000 to 10,000 r.p.m. sediment (IIIB) used in this study. It also suggests that, by using a combined sediment IIIB from carcinoma, sarcoma, and melanoma, this test could possibly detect all these tumours equally well and to a greater degree of accuracy than 90%.

It also seems feasible that by further fractionation of sediment IIIB one could hope to obtain a fraction which would distinguish malignant tumours from benign tumours. This, too, would be of great clinical usefulness. Sediment IIIB from an amelanotic melanoma with metastasis to the omentum was an exception; with this antigen both carcinomas and sarcomas were detected to a greater extent (80%) than were melanomas (75%). Could this observed difference in antigenic specificity be related to metastasis?

Studies with polysaccharide-like sensitizing substances (S.S.)—prepared from carcinoma sediments IIIB and used for immunization of guinea-pigs—show a broad antigenicity similar to that of its parent antigen. For example, a polysaccharide-like S.S. prepared from adenocarcinoma of the colon (sediment IIIB) shows common antigenicity with adenocarcinomas of the colon, breast, lung, and stomach, squamous carcinomas, melanomas, and fibrosarcoma. These studies are reported in the accompanying article (Makari, 1958).

The study of antigenic relationships between tumours is very fascinating but is still in its infancy. Two examples are given here to show how the Schultz–Dale test could be most helpful in such studies. In the guinea-pig immunized with carcinoma of the colon sediment IIIB (see Table IV) it was found that desensitization to carcinoma antigen prevented the sarcoma reaction, but that desensitization to sarcoma antigen allowed the later appearance of carcinoma reaction. We may assume that the two antigens have components in common, and that the horns immunized actively with carcinoma also contained, besides this antibody in common with sarcoma, another antibody or group of antibodies reacting only with carcinoma antigens.

In the second example (Table III) a few observations are of interest. Listing the tumours studied in order of their immunizing capacity, we find the spectrum of antigenic composition increasing in the following order: melanoma, carcinoma of the breast, carcinoma of the lung, squamous-cell carcinoma of the mouth, lymphosarcoma, fibrosarcoma, and, finally, recurrent lymphoma. If the supernatants are studied for antigenicity, however, we see a reversal of the order shown above, with the antigenic spectrum widening as we go from fibrosarcoma to lymphosarcoma and then to carcinoma of the lung and oesophagus. Melanoma of the skin is an exception. The sediment from carcinoma of the liver (secondary from breast) was prepared differently from the others by including the sediment at 3,000 r.p.m. to that at 10,000 r.p.m. It is surprising, however, that, despite this addition, there seems to be some loss of antigenicity of the sediment as compared with the other carcinomas tested. Again one wonders whether this difference may be due to the fact that the carcinoma of the liver is a metastatic lesion compared with carcinoma of the lung and carcinoma of the oesophagus, which are primary.

One more question: What should be the management of an individual with a positive tumour-screening test with no localizing symptoms or signs and in whom a thorough check-up is negative? One could still follow a "wait and see" policy and keep such a person under strict surveillance until the first signs and symptoms appear. This would necessarily mean a loss of both precious time and an excellent opportunity for cure. There is, in my opinion, another alternative—namely, the detection of circulating antigens from tumour-damaged organs by use of the Schultz–Dale test.

In preliminary experiments we have found it possible to detect liver antigen, kidney antigen, etc., in the serum by the use of normal liver and kidney antigens for immunization of guinea-pigs. On finding evidence of circulating kidney antigen—for example, in conjunction with a positive tumour-screening test or a positive diagnostic test—it becomes possible to diagnose not only the presence of a tumour and its type but also its location. In this way, despite the limitations of our present surgical techniques, operative intervention at such an early phase would result in much better chances of a cure.

Summary

The Schultz–Dale test described earlier (Makari, 1955) has been modified by immunizing guinea-pigs with carcinoma sediment obtained between 3,000 and 10,000 r.p.m. instead of 3,200 to 4,000 r.p.m. This modification has been studied in 566 individuals and 704 serum specimens obtained from blood-bank sera.

89% of 262 carcinomas, 73% of 130 malignant tumours other than carcinoma, and 94.2% of 35 benign tumours were accurately diagnosed. 77.9% of 59 pre-cancerous lesions and suspected tumour cases were positive, while only 12.5% of 80 healthy donors and 12.6% of 704 serum specimens obtained from the blood bank were positive.

This modification can be useful as a tumour-screening procedure, while the original method described by Makari and confirmed by Burrows would serve as a specific diagnostic test for carcinoma.

Some antigenic relationships between various tumours are also discussed.

I thank Dr. Peter Krag, of the State Serum Institute, Copenhagen, for his collaboration in the experiment shown in Table IV, and Mr. H. D. Hamilton, of the Muhlenberg Hospital, for his help in editing the manuscript. This work was done at the University of Texas.

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The Residential Care of Disturbed Children contains the introductory papers read at this year's annual conference for staffs of child guidance clinics sponsored by the National Association for Mental Health. The booklet is obtainable from the association at 39, Queen Anne Street, London, W.1. (43 pp.; 3s. 6d.)

COMPLICATIONS OF CANDIDA ALBICANS INFECTION IN INFANCY

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Thrush was first described in 1764 by Rosén von Rosenstein, who mentions a disease of the mouth, more severe if it spreads into the lungs. Thrush infections were later described by Langenbeck in 1839, Berg (1841), and Robin (1853). Robin called the organism *Oidium albicans*, and in 1890 Zopf renamed it *Monilia albicans*. From then until the present time the organism, now known as *Candida albicans*, has been adjudged to be responsible for disease in man. During recent years, since the discovery of broad-spectrum antibiotics, increased interest has been paid to the severe effects which may be produced. In infancy, thrush has long been known as a common disease occurring especially in sickly and undersized children. The majority of cases present an oral disease of varying severity, but many reports have been written of far more serious consequences of invasion by the fungus. These usually involve local spread to the gastro-intestinal or respiratory systems, but monilial septicaemia with metastatic disease is also described.

The purpose of this paper is to present four cases of thrush oesophagitis and to review previous writings on the complications and treatment of *Candida albicans* infections. Three of the cases present a very definite syndrome which is due to thrush, though the oesophagitis cannot be proved with certainty, and the fourth is a fatal case of thrush oesophagitis proved at necropsy.

Case 1

A male infant aged 26 days was admitted to hospital on November 10, 1956, with a history of cyanotic attacks and difficult breathing for five days. He had a full-term normal delivery but difficulty in sucking from birth. On the day of admission severe thrush was noted.

On admission he was a well-nourished infant weighing 7 lb. 2 oz. (3.2 kg.). He was very dyspnoeic (rate 60 a minute), was cyanosed, and had marked stridor and intercostal recession. His temperature was 98.4° F. (36.9° C.). There were rhonchi throughout both lung fields. He had a grade III systolic murmur in the fourth left interspace suggestive of a ventricular septal defect, but no signs of congestive cardiac failure.

He was nursed in an oxygen tent moistened with "alevaire" and given penicillin, 250,000 units six-hourly, streptomycin, 75 mg. twice daily, nystatin, 100,000 units six-hourly, and 0.5 ml. injections of vitamin B complex on alternate days. He was offered feeds of expressed breast milk.

X-ray examination of the chest (Fig. 1) revealed bilateral bronchopneumonia. A blood count showed a haemoglobin of 15.3 g. per 100 ml. and 11,700 white cells (polymorphs 47.5%, monocytes 0.5%, lymphocytes 51%, eosinophils 1%). An oral swab grew candida.

For a few days the child improved generally, though the thrush remained obvious. He then deteriorated rapidly, was cyanosed outside the oxygen tent, and had very pronounced blue attacks, mainly during feeding.

A "lipiodol"-swallow examination on November 21 (Fig. 2) showed pooling of the oil in the pharynx with spill-over into the lungs. An aspiration pneumonia affected the major portion of the right lung and the mid-portion of the left. It was then decided to take him off all oral feeds and medicines and to give him an intravenous drip. This treatment was continued for 10 days—the fluid containing appropriate electrolytes and vitamins, and plasma was given daily. His condition improved, his colour became pink, and all chest signs disappeared. On one occasion—three days after this treatment was started—he was fed and became extremely cyanosed. On November 30 a repeat lipiodol swallow (Fig. 3) showed easy passage from pharynx to oesophagus with no spill-over. The lung fields had almost cleared.

From December 1 slow oral feeding was resumed and he made an uninterrupted recovery (Fig. 4).

Case 2

A male infant aged 15 days was admitted to hospital on March 17, 1956. He had been quite well until he was 8 days old, when he developed thrush. This became worse in spite of treatment, and for a few days before admission he had been breathless and had vomited some of his feeds.

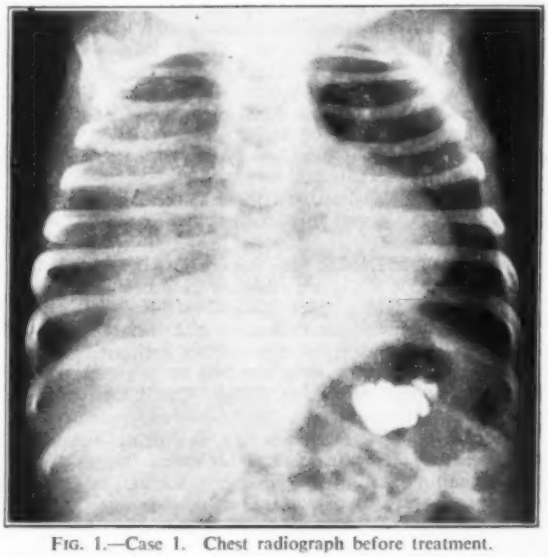

FIG. 1.—Case 1. Chest radiograph before treatment.

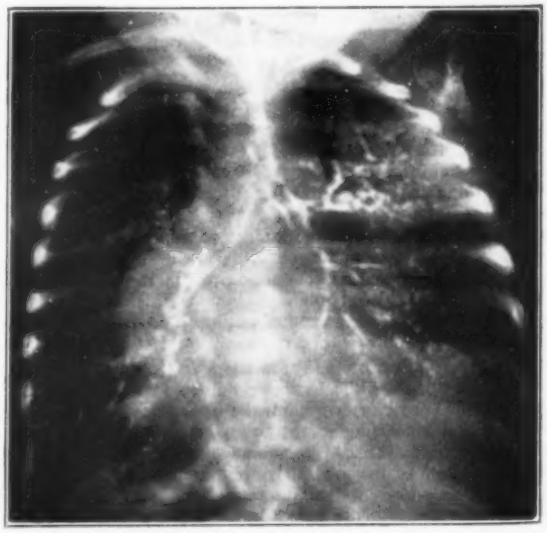

FIG. 2.—Case 1. Radiograph of lipiodol swallow before treatment.

On examination he was apyrexial but extremely ill, cyanosed, and dyspnoeic, and frothy mucus was bubbling from his mouth. His mouth was swollen and showed severe thrush with some ulceration. Chest examination revealed recession, and on auscultation rales and rhonchi were heard throughout both lung fields. On attempting to swallow he became very blue and regurgitated most of what was taken. A lipiodol-swallow examination showed a spill-over into the trachea and that some of the oil would not enter the stomach through the cardiac sphincter. This was thought to be due to reflex cardiospasm due to oesophagitis. Treatment was instituted immediately; oral feeding was entirely stopped and intravenous drip, penicillin, streptomycin, and nystatin (100,000 units, four-hourly) were given.

Two days later the child was a little better but still extremely ill, and hydroxystilbamidine, 10 mg. intravenously daily, was started. On March 24 oral feeding was again tried, but there was immediate deterioration. *X*-ray examination at this stage (Fig. 5) showed a right basal pneumonia. Intravenous therapy was again started, though small oral feeds were continued. The condition improved very gradually. On April 8 lipiodol-swallow examination was repeated, and on this occasion the oil passed rapidly from mouth to stomach without spill-over or hold-up.

The patient was discharged well on May 5.

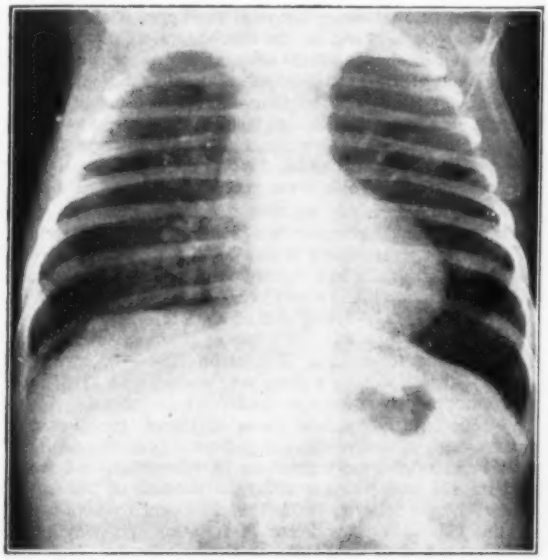

FIG. 3.—Case 1. Chest radiograph after treatment.

FIG. 4.—Case 1. Radiograph of lipiodol swallow after treatment.

Case 3

A female patient aged 5 weeks was admitted to hospital on January 7, 1954. She had a normal history until 3 weeks of age, when she developed thrush of the mouth, which was treated daily with 1% gentian violet without improvement, and then unsuccessfully with chlortetracycline. She had been very difficult about taking feeds throughout this period. For one day she had had a cough.

On admission her temperature was 101° F. (38.3° C.), but she appeared to be fairly well. She was not cyanosed or dyspnoeic, but she dribbled continually from her mouth. Her chest was clinically quite clear. There was very marked thrush of the mouth. She was treated with penicillin, "bejectal," and local gentian violet. Two days later the mouth was worse and local chlortetracycline was tried. The mouth remained unhealthy, and on January 15 signs of severe pneumonia were present clinically and were confirmed by *x*-ray examination (Fig. 6). The plates were reported as being unlike moniliasis of the lungs. Following this, her condition deteriorated rapidly in spite of oxytetracycline and chloramphenicol. It was noted that feeding caused marked distress and cyanosis. She died on April 22. Unfortunately necropsy was refused.

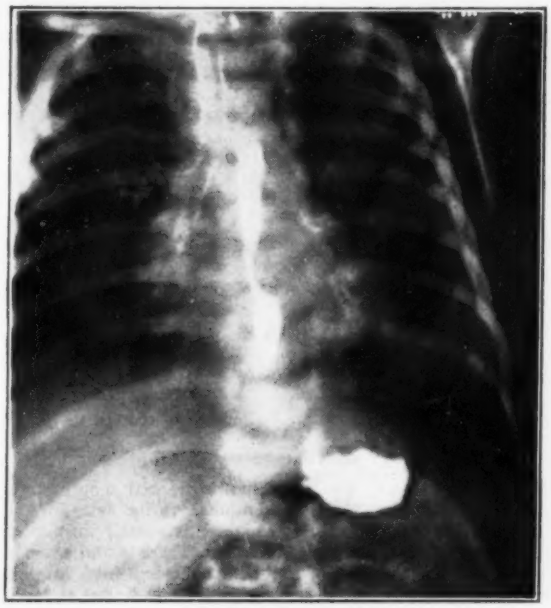

FIG. 5.—Case 2. Radiograph taken during treatment.

Case 4

A male infant aged 9 months was admitted to hospital on April 21, 1952. His history was of a normal child until four days before admission, when he developed vomiting and an acute diarrhoea. These symptoms were not improving, so he was brought to hospital. On examination his temperature was 102° F. (38.9° C.); he was dehydrated and showed signs of malnutrition. His weight was 12¼ lb. (5.7 kg.). Other positive signs found were severe thrush of the

mouth and pharynx and rhonchi throughout the lungs. Both the liver and the spleen were just palpable.

He was given intravenous fluids, intramuscular penicillin and streptomycin, and gentian violet was used locally. Oral feeding of skimmed milk and water was begun after 24 hours. Initially he improved on treatment, but the thrush never cleared. On April 30 he was noticed to be jaundiced, rather chesty, and cyanosed, and his chest was full of rales. His temperature rose to 103° F. (39.4° C.). After this his condition rapidly worsened, and he died two days later.

Necropsy showed a dehydrated child, with marked thrush of mouth and pharynx. The lungs showed basal congestion. The oesophagus was thickened and the surface covered with thick white granular membrane which stopped short at the entrance to the stomach. Histology of the oesophagus showed acute inflammatory changes with exudation and superficial necrosis, and on Gram's stain the presence of *C. albicans*.

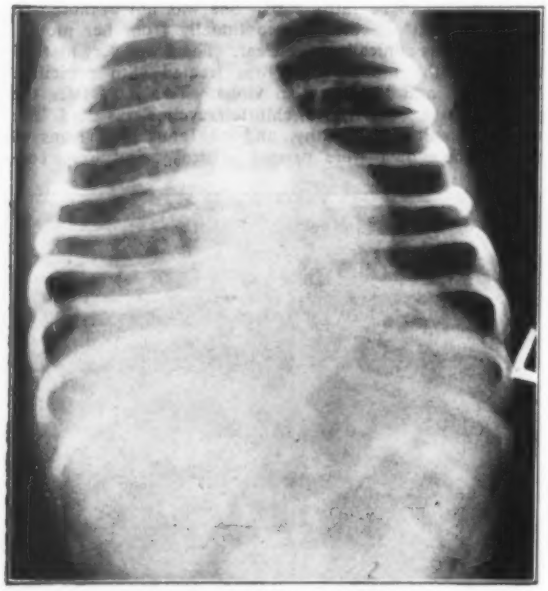

FIG. 6.—Case 3. Radiograph of chest.

Aetiology and Frequency of Moniliasis

C. albicans may be found in the normal mouth flora, especially in older children and adults. In the newborn and infants, where the oral *p*H is high, it is usually introduced from the exterior and causes disease. There is an increased incidence in children of mothers suffering from vaginal moniliasis. This has been observed many times, and one experiment was done to prove that vaginal thrush could be introduced into the mouth of the newborn, producing disease (Hesseltine *et al.*, 1934). Some nurseries have reported an incidence of infection as high as 18.2%. Apart from vaginal thrush as a cause, many cases must be produced by direct spread due to nurses' fingers, bottle teats, dummies, etc. Any trauma to the oral mucosa will increase the likelihood of infection. Airborne infection seems to play no part in the spread.

In any age group the use of broad-spectrum antibiotics has increased the incidence of moniliasis.

Complications of Moniliasis

Oral thrush, which in itself can be a severe disease interfering seriously with nutrition, can spread to cause three types of disease: (1) spread into the gastro-intestinal tract, especially the oesophagus; (2) spread into the lungs; and (3) systemic spread.

Gastro-intestinal Spread

As gastro-intestinal spread is the main topic of this paper it is dealt with in more detail than the other complications, especially as regards oesophagitis. The diagnosis of oesophagitis in Cases 1–3 cannot be proved. However, the syndrome which they represent is a definite one whether it be due to actual spread to the oesophagus, as some authorities have felt, or to an incoordination of swallowing due to thrush of the posterior pharynx, either leading to inhalation of food and aspiration bronchopneumonia. This syndrome may be described as one in which a baby with oral thrush becomes very toxic and sometimes dehydrated, has difficulty in swallowing, and during feeds is noted to choke and become cyanosed. Within a short period a severe bronchopneumonia develops, and without active treatment death may easily follow, as happened in Case 3. To substantiate the diagnosis *x*-ray films of the chest will show marked bronchopneumonia, and lipiodol swallow an incoordination of swallowing either at the upper (Case 1) or at the lower (Case 2) end of the oesophagus. Culture of the oral flora can show that *C. albicans* is present, but not at what level of the gastro-intestinal tract. Some authors working on adults with similar clinical pictures have performed oesophagoscopies on their cases, and shown that the oesophagus is involved in a disease similar to that in the mouth (Stenderup *et al.*, 1956). Such an investigation was not thought safe in these very ill babies.

In the literature this syndrome is well described. Ebbs (1938) performed necropsies on 28 infants under 10 months of age, the average being 4 months, all of whom had died of oesophagitis: 22 had thrush oesophagitis. The clinical picture in these children was very similar to that described above. Reye (1941) found that of 150 necropsies 10 showed oesophagitis, which was the cause of death in seven and in five was due to thrush. Henderson (1943) reviewed 163 cases of thrush during a three-year period, and 13 of these had oesophagitis and seven died from its effects. Adams (1944) described five fatal cases of thrush pneumonia in infants with a similar clinical picture. Lederer and Todd (1949) did routine necropsies on 28 infants under 4 weeks and on 176 under 1 year of age. In seven of the former and 19 of the latter moniliasis was thought to have caused death. Clinically a syndrome of vomiting and dehydration with aspiration of vomit and septicaemia is described. Six patients died suddenly from blocking of the respiratory passages.

Wolff *et al.* (1955) describe two cases identical with our Cases 1–3. Both responded well to similar treatment. Andrén and Theander (1956) and Geiger *et al.* (1946), writing on two adults, mention typical *x*-ray changes of oesophageal moniliasis. Both had been on long courses of antibiotics and were *x*-rayed because they had oral thrush with dysphagia. The entire thoracic oesophagus was irregular and ragged, and was made up of numerous small indentations and protrusions. Longitudinal folds were discernible and the lumen became distended on passage of a large bolus. Stenderup *et al.* (1956) had three adult patients with thrush, and in two oesophagoscopy showed thick coating of the oesophagus with monilia-like lesions.

Two authors mention intestinal moniliasis. MacGregor and Henderson (1943) examined two children found dead at home in whom marked intestinal thrush was present, and Zimmerman (1950) quotes a personal communication from Dr. Sydney Farber of five cases of disseminated moniliasis in childhood in which the primary site was the oesophagus or the intestines.

Thrush oesophagitis is a reasonably common disease, and, though for many years it was thought to be diagnosable only at necropsy, there is no doubt that it can be diagnosed and treated during life.

Broncho-pulmonary Moniliasis

Much controversy has arisen whether primary moniliasis of the lungs exists or not. From the first mention of the

condition by Castellani in 1905 until now, many authors have published reports of cases. Many, however, feel that there is no such disease and that where moniliasis is found in the lungs it is a secondary infection. Actual proof of moniliasis is made difficult by two factors—that it is hard to prove that a positive candida culture comes from the lungs when oral moniliasis is present, and that after death moniliasis is a common secondary infection of tissues. There is no doubt, however, that at any age oral thrush can be complicated by pneumonia, which is not always due to inhalation. Some cases—for example, that described by Beckmann *et al.* (1955) with prompt response to nystatin, and the fatal case described by Falkmer and Wising (1955) —are very convincing cases of primary broncho-pulmonary thrush. Sahni (1957) describes a case without primary lung disease in which the patient responded adequately to treatment with potassium iodide and nystatin. It seems that pulmonary moniliasis must be regarded as a serious complication of the oral disease.

Systemic Moniliasis

A number of cases have been described of septicaemic spread of candida infection, with widespread lesions developing. References to the following cases were found:

Two patients with monilia meningitis, one of whom was found to be quite well after a four-year follow-up (Fine *et al.*, 1955; Carnu and Charanis, 1954).

A patient who died of thrush and was found at necropsy to have a perinephric abscess, thrombosis of the inferior vena cava, and bronchopneumonia, all growing pure *C. albicans* (Brown *et al.*, 1953).

A patient who at necropsy had multiple abscess of the brain, myocardium, and kidneys due to monilia (Brown *et al.*, 1953).

Two further cases quoted by Brown *et al.* were found at necropsy to have monilial abscesses of myocardium, kidneys, and lungs. Blood culture grew *C. albicans* in one case and *C. tropicalis* in the other. Both cases had had long courses of broad-spectrum antibiotics.

Zimmerman (1950) quotes the case of a patient who died of mycotic endocarditis, and mentions a personal communication from Dr. Sydney Farber quoting five cases of disseminated moniliasis in children being treated with various chemotherapeutics, and at necropsy there were widespread fungus lesions. The primary site in all was the oesophagus or intestines.

Geiger *et al.* (1946) quote another fatal case of *C. albicans* endocarditis.

Although these are not a vast number of cases, they do present a frightening aspect of the possible outcome of thrush.

Pathology

Case 4 illustrates the pathology of thrush oesophagitis. The organism grows as patches of greyish-white membrane on the mucous surfaces, this membrane consisting of a tangled growth of Gram-positive hyphae with spores produced at the junctions of the segments. Permeation and destruction of the epithelium occur and often there is secondary bacterial growth. The oesophagus is either primarily involved or involved through secondary extrusion from a contiguous lesion. There may be either superficial erosion or actual pseudomembrane formation with mycelial threads found in the tissue sections.

Treatment of Moniliasis

In the majority of simple cases of not very ill children with oral thrush local measures will suffice. These consist of gentle handling so as not to traumatize the mucosa, and swabbing with at most three daily applications of 1% gentian violet solution. If this is ineffective, and in more severe cases, drug therapy should be started. The possibilities in this direction are:

Nystatin, an antifungal agent derived from cultures of *Streptomyces noursei*, in doses varying from 50,000 units four times daily in the newborn to 500,000 units in adults, has proved a very powerful antimonilial weapon. It has eliminated or reduced the number of candida organisms in the stools of 25 adult patients in 48 to 72 hours (Sternberg *et al.*, 1953–4). It is poorly absorbed from the gastro-intestinal tract and is mainly of use locally. There are few or no toxic effects.

Hydroxystilbamidine, which is one of the aromatic diamidine compounds and has been used in various mycotic infections, was found useful by Wolff *et al.* (1955) in two cases of thrush oesophagitis. The dosage suggested is 5 mg. per kg. given 12-hourly for four to six days. Toxic effects, such as trigeminal neuralgia and renal damage, which are common with stilbamidine therapy, have not been reported. There is a marked tendency to thrombophlebitis of the veins used for the intravenous injection, and there are reports of weakness and even circulatory collapse following the injection. In a series of three cases in adults pentamidine was found very effective (Sutliff *et al.*, 1954).

Brilliant green has been successfully used locally, intravenously, and by aerosol in cases of pneumonia. The suggested dosage for intravenous use is 0.16 to 0.5 mg. per kg. daily, and by aerosol 2 ml. of 0.1 to 0.2% solution in 50% propylene glycol by oxygen inhalation.

Potassium iodide has been effectively used in many cases, but largely in conjunction with other drugs.

"Paraben" (parahydroxybenzoic acid) has been used experimentally in moniliasis caused by chlortetracycline and found to be effective. So far it has not been found useful therapeutically, but it may be in the future. It is a substance used to prevent fungus growth in foods.

Recently other chemotherapy has been successful in some cases. (*a*) 1,2,3,4-Tetrahydrofluorenon (T.H.F.) was tried with excellent results in a child with lung thrush following a skin infection (Lindguist, 1957). He reports a series of 30 cases treated by A. Frisk with favourable results in 50%. (*b*) 2.2-Dihydroxi-5.5-dichlordiphenylsulphide has been used systemically with success in one case. It was previously used only locally (Richter, 1950). (*c*) Sodium caprylate has been used in two cases (Keeney, 1946).

Additional and supportive therapy varies according to the complication present. Difficulties of feeding are obvious in cases of oral thrush, as is the need for oxygen in pneumonia. The vital stopping of all oral feeding in cases such as those described here must be borne in mind and instituted before fatal inhalation pneumonia occurs. Intravenous therapy must be continued until a lipiodol-swallow examination shows the baby is able to swallow properly.

Summary and Conclusion

Four cases of thrush oesophagitis are described; two patients survived and two died. An attempt is made to describe the clinical syndrome related to this complication of thrush and how it should be treated. There is a review of cases described with one or more of the complications of oral thrush and their outcome. The possible therapy and the pathology of the condition are outlined.

Whilst oral thrush is an extremely common condition in newborn and infants' wards, the severer complications are not so well known, and as therapy may be life-saving, especially in cases of oesophageal spread, an attempt is made to review some of these complications. Thrush oesophagitis, or a syndrome as cited to it, is fairly common, and often fatal if unrecognized or incorrectly treated. The entity of monilia bronchopneumonia definitely exists, whether as a primary or a secondary disease. Rarer complications, especially monilial septicaemia, are worth remembering, though they are mainly diagnosed at necropsy.

One feels that no case of oral thrush should be regarded light-heartedly until all traces of the disease have cleared up and one is certain no complications have developed.

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AMIPHENAZOLE AND MORPHINE IN PRODUCTION OF ANALGESIA

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Shaw and Bentley (1952) were the first to point out that a dog completely narcotized with morphine (and sometimes hyoscine) could be restored to normal within a few minutes by an intravenous injection of 2 : 4-diamino-5-phenylthiazole (amiphenazole ; " daptazole," DHA 245). The most interesting part of this phenomenon was the complete restoration of consciousness of the dog. This work has been confirmed (Gershon and Shaw, 1958). It was also shown that the analgesia produced by the morphine was not affected by the amiphenazole.

By means of the use of amiphenazole, large doses of morphine (up to 200 mg. q.i.d.) were given to patients suffering from intractable pain in terminal carcinoma (Shaw and Shulman, 1955 ; McKeogh and Shaw, 1956). This use of the combination of morphine and amiphenazole has continued in Melbourne for a period of nearly four years. The same excellent results have been obtained in about 500 patients. The combined drugs have been used by others in a similar manner (Hügin, 1956 ; Holmes, 1956 ; Hayward-Butt, 1957 ; Dundee, 1957 ; Overton, 1957).

These early results led us to believe that amiphenazole was a morphine antagonist similar in nature to nalorphine, etc., with the exception that the analgesia was not antagonized and that amiphenazole had no side-effects when given alone. Recent work by us (Christie *et al.*, 1958) has led us to modify this view.

It is the purpose of this paper to explain the exact nature of the action of amiphenazole. In a previous paper (Christie *et al.*, 1958) we had shown that amiphenazole had little influence on morphine-induced nausea and vomiting. Cyclizine chloride (" marzine ") is the drug of choice here. Amiphenazole has an irregular stimulating action on an already established morphine-induced respiratory depression when given as a single dose. Although Shulman and Trethewie (1956) refer to amiphenazole as a respiratory stimulant, others have noted its unsatisfactory respiratory stimulant action, and on this account have dismissed the drug as being valueless as a morphine antagonist (Bonnycastle and Costa, 1955).

Our approach to the problem has been to obtain objective evidence that amiphenazole does influence the action of morphine. The main approach has been through psychological testing. Unfortunately, the material at our disposal, elderly and failing cancer patients, has not remained in a constant state long enough to enable adequate controls to be used. The difficulty of carrying out such work on healthy volunteers has been stressed earlier (Christie *et al.*, 1958). Although the psychological testing has been of help to us, we have had to rely more on the observations of trained personnel, nursing and medical, and especially the medical specialists in charge of the cases. We would be the first to admit the inadequacy of such evidence, but we are impressed with the unanimity of opinion expressed despite staff changes which occurred over a period of four years. One of the members of the present team is an experienced psychologist.

In all, 27 cases have been assessed for the work. Below are given case histories of 10 patients whose condition and responses permitted the nearest approach to a controlled experiment. The remaining 17 cases showed aspects similar to these, but the results were neither so clear nor so extensive.

Material and Methods

The series consisted of 27 patients with intractable pain of terminal carcinoma. The sexes were about equally represented. No attempt was made to classify the type of malignancy. Similarly, the assessment of pain was on a subjective basis. While this method may be open to objections, nevertheless it was felt that the duration and extent of the pain made the results more reliable than they would be, for instance, in post-operative pain.

Psychological Testing.—As has been mentioned, two major obstacles are encountered in obtaining measures of the behavioural changes which are indicated by clinical observation: (*a*) patient impaired by illness, and (*b*) lack of tests known to be sensitive to these changes. Several techniques were attempted, however, and these have provided indications that the effects are measurable and may be better

handled by other techniques being developed at present. The techniques used were (1) Wechsler (1945) memory scale; (2) hand steadiness (Hill and Belleville, 1953); (3) sections of Wechsler adult intelligence scale (Wechsler, 1944)—(*a*) arithmetic (time score and accuracy), (*b*) digit span, (*c*) Koh's block design test (time score and accuracy); (4) spiral after-effect test (Price and Deabler, 1955).

Clinical Assessment Procedure.—The patients were under continual observation by the nursing staff. One of the sisters in charge of one of the wards had occupied this position for four years before the introduction of the combined drug therapy and has continued in the same position for the four years since the beginning of the treatment. The patients were seen at least twice a week by three of the authors (S. G., N. O., F. H. S.). The procedure we endeavoured to follow was to start the patients on morphine, which was given in increasing amounts over the next few days until complete 24-hour analgesia was achieved by injections at six-hourly intervals. When the patient showed a marked drowsiness or narcosis (or respiratory depression) amiphenazole was introduced and the patient kept under observation. At a later date the amiphenazole was withdrawn abruptly and again careful observation was made. When a change had been observed amiphenazole was reintroduced.

Case Reports

Case 1.—Man aged 65. *August 9, 1957:*—Morphine, 65 mg. q.i.d. Lethargic and unable to concentrate but not depressed; well oriented. *August 16:*—Morphine, 100 mg. q.i.d.; amiphenazole, 60, 60, 20, 20 mg. (given with the morphine at six-hourly intervals in the dosages indicated). Much more active conversation, more confident. Reads the paper and takes interest in the news. Well oriented. *September 11:*—Morphine, 100 mg. q.i.d.; amiphenazole, 60, 60, 20, 20 mg. Quite alert and even a little aggressive. *September 24:*—Morphine, 100 mg. q.i.d.; amiphenazole, 20, 20, 0, 0 mg. No interest in anything. Very little contact with events around him. The reason for the reduction in the amiphenazole was the fact that the patient fully appreciated his hopeless state and it was considered more humane to have him partly narcotized. *October 4:*—Morphine, 100 mg. No amiphenazole. Patient narcotized. *October 6:*—Died.

Case 2.—Man aged 20. *July 2, 1957:*—Morphine, 15 mg. q.i.d. Cheerful; reads and draws, but is drowsy most of the time and has some difficulty in focusing. Well oriented. *July 9:*—Morphine, 20 mg. q.i.d. Awakens in semi-dream state. Great difficulty in focusing. Cannot concentrate enough to read and understand, but if pressed can read out words. *July 16:*—Morphine, 20 mg. q.i.d. One day without morphine had been tried, but withdrawal syndrome started, so returned to full dose. Given hand steadiness test; then put on amiphenazole, 60, 60, 40, 20 mg., and morphine, 20 mg. q.i.d. *July 19:*—Claims to be feeling better, but still has some difficulty in concentrating. Hand steadiness test repeated; very significant improvement ($P=0.005$). Remained alert until near death, when amiphenazole was discontinued because awareness of his condition caused distress.

Case 3.—Man aged 55. Patient was a morphine addict of 12 years' standing. He had often tried to stop, but always experienced such a severe withdrawal syndrome that he was afraid to try again unaided. Previous attempts with methadone and corticotrophin had not given freedom from the discomfort. Sudden total withdrawal with amiphenazole (see record below) produced no effect at the time, although later, when the patient was told that he had been taken off on a certain day, he recalled slight symptoms, but so much less than he had ever felt before that he had not really noticed them. *November 23, 1957:*—Morphine, 65 mg. q.i.d. Very lethargic, with slow, slurred speech; not very talkative, but co-operative in tests. Given arithmetic, digit span, Koh's block design test, and spiral after-effect test. *December 3:*—Morphine, 65 mg. q.i.d.; amiphenazole, 50 mg. orally and 10 mg. intramuscularly q.i.d. More active, and brighter speech. Generally alert and interested in progress. Tests repeated. *December 15:*—Amiphenazole, 20 mg. intramuscularly q.i.d. Morphine abruptly stopped. Has shown no sign of withdrawal syndrome. Is even brighter and more normal than on November 23. Claims to have had his "first good night's sleep." Tests repeated. *Test results:*—Although there are not enough for statistical treatment, the trend is interesting. Arithmetic: time taken decreased by 43% between the first two trials and by another 22% between the second and third trials. Digit span: number remembered increased slightly over the three trials. Blocks: time taken decreased by 19% over first two trials, and the third was the same as the second. Spiral after-effect: time of effect increased from first to second, but decreased from second to third. This latter may have been due to some barbiturate which he had received the evening before testing.

We have treated one other morphine addict (female) in the same manner with the same successful result.

Case 4.—Spinster aged 50. *July 16, 1957:*—Morphine, 15 mg. q.i.d. Feels much more sleepy than usual, but can concentrate on embroidery. Given hand steadiness test. *July 19:*—Morphine, 15 mg. q.i.d.; amiphenazole, 20, 20, 20, 20 mg. Feeling brighter and much less sleepy. Expressed surprise that she was no longer sleeping during the day. Ward staff also commented on this; hand steadiness test repeated and showed improvement which is almost significant ($P=0.07$). Continued on morphine and amiphenazole for two months. Morphine stopped because patient no longer had pain. She remained bright and alert over whole period, with no withdrawal syndrome.

Case 5.—Married woman aged 60. *February 18, 1958:*—Morphine, 100 mg. q.i.d.; amiphenazole 60, 40, 40, 20 mg. This patient has been on the above medication for many months and has been bright, cheerful, and alert throughout. She walks about freely, both in her ward and in the grounds, and reads papers. Clinically, the addition of amiphenazole has made her bright and alert, whereas before its addition she was very drowsy, unable to read, and remained bedridden. Clinical condition (gross basal-cell carcinoma involving half the face and palate) precluded valid testing. *April 18:*—Patient on same dose of morphine and amiphenazole, and condition unchanged.

Case 6.—Man aged 70. *October 9 and 14, 1957:*—Morphine, 50 mg. q.i.d. Very depressed and always complaining. On the verge of weeping, and wanting to die. *November 7:*—Morphine, 65 mg. q.i.d.; amiphenazole, 60, 60, 40, 40 mg. Considerably brighter and admits feeling better. *November 19:*—Morphine, 100 mg. q.i.d.; amiphenazole, 100 mg. b.d. Well oriented, but depression returned, although not quite so bad as on November 7. Condition continued thus until *February 10, 1958:*—Morphine, 145 mg.; amiphenazole, 200, 200, 150, 0 mg. Within several days of this amiphenazole increase he was completely changed in his mood and general outlook. He volunteered for the first time that he felt much better and thanked the doctors for what they had done. There was a great change from the previous irritable, dissatisfied attitude, with depression, weeping, and hypochondriasis—being quite cheerful and confident. This condition continued for six weeks. *March 31:*—The patient said he required no more morphine, so it was discontinued abruptly. No withdrawal symptoms appeared. *April 3:*—Complained of pain; morphine, 65 mg. b.d., given with amiphenazole, 200, 200, 150, 0 mg. Pain controlled. *April 10:*—Patient's condition worse. Morphine discontinued; amiphenazole continued. No pain; no withdrawal symptoms. *April 14:*—Patient's condition improved again.

Case 7.—Man aged 57. *November 12, 1957:*—Morphine, 50 mg. q.i.d.; amiphenazole, 40, 40, 20, 10 mg. Had been put on to amiphenazole because he was so sleepy that he could not keep awake for visitors. On amiphenazole he was much wider awake. *November 19:*—Morphine, 50 mg. q.i.d.; no amiphenazole. Feeling sleepy all day and could not talk to visitors; unable to read the paper. *Novem-*

ber 28:—Morphine, 50 mg. q.i.d.; amiphenazole, 20, 100, 100, 10 mg. Brighter, no longer drowsy, and able to converse with visitors and read easily. *November 30*:—At this point amiphenazole was discontinued and he became drowsy again and unable to stay awake for visitors or to read. *December 3*:—Restored to amiphenazole, 40, 120, 120, 10 mg., and again became bright. This patient's level of alertness could be altered at will by altering the dose of amiphenazole which accompanied his morphine.

Case 8.—Married woman aged 56. This patient had risen slowly to a dose of morphine, 110 mg. q.i.d., with amiphenazole, 40, 40, 20, 20 mg. She was taken off amiphenazole; after 10 days on this dosage of morphine alone, she appeared normal except for slight nausea and tremor. However, further questioning and administration of the Wechsler memory scale showed gross confusion and disorientation of a type typical of a brain lesion or toxic psychosis. She was incapable of performing any task properly. She was given amiphenazole, 60, 60, 40, 40 mg., and over a week she recovered until she became indistinguishable from a normal person. Her Wechsler memory scale corrected score rose from 66 to 98 over that week. It was thought unethical to repeat withdrawal of amiphenazole. This patient has continued medication with morphine and amiphenazole until the time of writing (May, 1958), and at no time has there been a recurrence of an episode similar to that when taken off amiphenazole.

Case 9.—Married woman aged 55. For some weeks this patient was maintained successfully on morphine, 15 mg. q.i.d., with amiphenazole, 50 mg. q.i.d. The patient's liver became enlarged and jaundice appeared, soon after which there was a sudden onset of drowsiness. Amiphenazole was increased from 100 mg. to 150 mg. to 200 mg. q.i.d. with no effect. Respirations dropped to 6 a minute. Death occurred one week after the onset of the drowsiness. At necropsy the liver weighed 2,800 g. and showed almost complete replacement by growth.

Case 10.—Man aged 60. For some weeks maintained successfully on morphine, 15 mg. q.i.d., with amiphenazole, 80 mg. q.i.d. A sudden onset of drowsiness coincided with a very tender enlarging liver. Morphine was discontinued except occasionally at night, but amiphenazole continued. No improvement occurred and the liver continued to enlarge. Death occurred just under one week after the onset of drowsiness. At necropsy the liver weighed 2,150 g. and showed diffuse nodular secondaries.

Up to date, five cases which closely follow the pattern of Cases 9 and 10 have been observed. In the latter cases, after the enlargement of the liver the onset of drowsiness could be predicted in each case, and this was not controlled by an increase in the amiphenazole dosage.

Discussion

The 10 case histories given are illustrative of the results which have been obtained with 500 patients over a period of four years. The following points can be made with a considerable degree of certainty.

In the presence of amiphenazole: (*a*) Morphine may be given in large doses (200 mg. q.i.d.) without any risk to the patient, provided the usual small doses are given at first. The dosage can be increased rapidly over a few days. (*b*) Drowsiness does not develop unless there is gross liver damage. The degree of alertness of the patient can be controlled by varying the dose of amiphenazole. (*c*) Addiction to morphine does not develop. This can be stated for the following reasons: (1) euphoria is absent, (2) no patient has ever expressed a craving, and (3) in at least four cases in which morphine (over 65 mg. q.i.d.) has been given for months there were no withdrawal symptoms on abrupt cessation of morphine administration. (*d*) Complete analgesia for 24 hours in the day can be obtained. The psychological value of the patient's never experiencing pain cannot be stressed too much. (*e*) It is necessary to reduce the dose of amiphenazole at night, otherwise the patient will complain of insomnia. (*f*) In certain cases, where the patient becomes aware of the hopelessness of his condition and when the downhill progress is rapid, it is necessary to omit the amiphenazole.

The mechanism of the combined role of morphine and amiphenazole is still unknown. A tentative hypothesis is that morphine and amiphenazole combine, probably in the liver, to form a non-narcotic analgesic substance. The evidence for this is that (1) the beneficial effect of the addition of amiphenazole to a drowsy patient already receiving morphine usually takes several hours to become apparent—for example, amiphenazole has only limited value in controlling the respiratory depression and vomiting induced by *single* doses of morphine (Christie *et al.*, 1958); (2) patients with liver damage do not derive benefit from amiphenazole; (3) patients suddenly deprived of morphine do not show withdrawal symptoms—that is, they are not really deprived of morphine but of the new compound (morphine and amiphenazole), and this deprivation does not lead to withdrawal symptoms; and (4) a similar suggestion would explain the lack of addiction.

This hypothesis, if correct, would indicate the method to be employed in the post-operative use of morphine and amiphenazole. About two days before the operation several small doses of morphine and amiphenazole should be given. Then immediately in the post-operative period the dose of morphine (with amiphenazole) could be increased to the desired degree to produce complete analgesia for intervals of six to eight hours as long as the pain continues (see Weber, 1958).

It should be particularly noted that the doses of amiphenazole used at present are much greater than those previously recommended. As much as 200 mg. may be given t.i.d. or q.i.d., either orally or intramuscularly.

More recently (Gershon *et al.*, unpublished) it has been shown that large doses of amiphenazole (up to 200 mg. a day) will relieve mild depressive states. This action would offer another explanation for the anti-narcotic effect of amiphenazole.

Summary

The beneficial effect of amiphenazole in preventing drowsiness or narcosis when large doses of morphine are administered in intractable pain of terminal carcinoma has been confirmed.

Addiction does not develop, so that the morphine may be withdrawn at any time without the production of withdrawal symptoms.

Case histories supporting the above conclusions are presented.

A tentative hypothesis for the mode of action of amiphenazole is advanced.

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PETROL-VAPOUR POISONING

BY

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In view of the widespread use of petrol it is surprising that deaths from inhaling the fumes are so rare. Petrol or gasoline vapour has been known for many years to be poisonous. In the reports of the Chief Inspector of Factories for 1937–47 four deaths due to gassing by petrol vapour have been recorded (Ministry of Supply, 1952).

I have been unable to find an account of death from petrol vapour in British medical journals, and so think the following accident worth recording, as many workers both inside and outside the medical profession are unaware of the lethal properties of the vapour.

Case Report

At a non-medical research laboratory in which petrol was used experimentally it was the custom for laboratory assistants to go to a hut 20 yards (18 metres) from the main building and fill a 2-gallon (9-litre) can with petrol. The petrol was kept in a poorly ventilated hut in a 40-gallon (180-litre) metal drum. The drum stood 33 in. (84 cm.) in height and was kept covered with a tightly fitting metal lid.

At 2.30 p.m. on a hot day a youth of 17, 5 ft. 6 in. (167 cm.) in height, was sent to fetch petrol. As he had not returned at 3.15 p.m. a messenger was sent, who found him dead, slumped with his head, shoulders, and arms over the edge of the drum. There was 9 in. (23 cm.) of petrol in the drum, and the youth had apparently placed the can inside the drum and had been ladling petrol with a beaker into the can.

At necropsy irregularly shaped areas were present on the right forearm and wrist where the superficial epithelium had disappeared, leaving dark-red areas. These excoriations involved areas on the upper arm and round the elbow, and resembled the raw areas seen on the body of a macerated stillborn foetus. Several similar smaller areas measuring up to 1 cm. in diameter were present on the forehead. There was slight bruising over the right anterior-superior iliac spine and on the right side of the abdomen, probably caused by pressure from the edge of the drum.

The body was pale and cyanosed; there were no external haemorrhages. The stomach contained semi-digested food, and the oesophagus and the trachea regurgitated stomach contents. Nothing else abnormal was found. There were no petechial haemorrhages in the lungs, heart, or thymus, nor were there any other signs of asphyxia. The internal organs were not congested. No smell of petrol was noted from the lungs. Microscopically the lungs, liver, heart, and kidneys were normal.

Inquiries showed that other workers, when getting petrol from the drum, left the can on the floor and ladled petrol out without stooping down and putting their heads into the drum. The dead lad could not do this, as he was not tall enough, but apparently had to bend his head and shoulders into the drum.

Discussion

Machle (1941) exhaustively reviews the subject of death from inhalation of petrol vapour and gives many references to American and Continental sources.

Petrol is a mixture of hydrocarbons of varying volatility and toxicity. Octane, which is present in high proportions in some petrols, is very toxic. N-octane is about seven times as toxic as pentane (Lawrence, 1945). Some commercial petrols contain benzine and other aromatic hydrocarbons which are of still greater toxicity. In Great Britain petrol contains 0.8 ml. of tetra-ethyl lead (T.E.L.) per litre (Ministry of Supply, 1952).

Poisoning by petrol vapour occurs rapidly by inhalation but slowly by ingestion. There is probably some skin absorption, but this is generally masked by the accompanying absorption through the lungs, which is the main factor in poisoning. Vigdortschik (1933) states that a concentration as low as 110 to 450 parts per million may produce symptoms in susceptible persons. Fieldner *et al.* (1921) found that 7,000 p.p.m. when inhaled produced definite intoxication in five minutes. Rambousek (1913) states that higher concentrations of the vapour cause almost immediate unconsciousness and death from respiratory arrest.

Machle (1941) records that men exposed to 1,000 p.p.m. showed drowsiness, dullness, and numbness at the end of 15 minutes, followed by vertigo, ataxia, and slight nausea after an hour. Symptoms occurred much more quickly after exposures to 3,000 p.p.m., while exposures to 7,000 p.p.m. caused intoxication in five minutes. Little is known about the concentration of petrol vapour that causes death in man after a short exposure. Machle records that a concentration of 10,000 p.p.m. is rapidly fatal in experimental animals. If the concentration of the vapour is high, absorption through the lungs may be very rapid and symptoms may appear within a few minutes of exposure. The type of coma appears to depend on the chemical nature of the petrol; paraffin hydrocarbons produce quiet coma, as shown by animal experiments, while unsaturated hydrocarbons cause convulsions (Haggard, 1920). The inferential evidence seems to be that the vapour contains a poison affecting the central nervous system. After a few minutes' exposure to a high concentration of vapour the victim passes into coma and dies without any respiratory struggle or post-mortem signs of anoxia (Machle, 1941).

The day of the accident was warm, favouring the formation of petrol vapour. Since the vapour is heavier than air, it seems certain that a heavy concentration formed in the closed drum. This was confirmed by the following test. In the early afternoon of a warm day in circumstances similar to those of the day of the accident an operator about the same height as the dead youth was equipped with an antiboys hose mask apparatus; the free end of the breathing hose was placed well outside the hut. The concentration of the petrol vapour was measured by a Poole combustimeter. So as to obtain samples of air from a wider area than that occupied by the end of the rubber suction tube the end of the tube was attached to a 2½-in. (6.3-cm.) funnel. The funnel was then attached to the operator so that the opening of the funnel was within a few inches of where his mouth and nose were when covered with a mask. The lid was removed from the drum, which contained 9 in. (23 cm.) of petrol. The operator then proceeded to fill the can with the beaker. To do this he had to keep his head and shoulders well in the drum. Fifteen seconds after the lid was removed the petrol-vapour concentration was found to be 25,000 p.p.m. During the next 80 seconds, while the can was being filled, the concentration of petrol vapour varied from 8,000 to 35,000 p.p.m., averaging about 20,000 p.p.m. The higher values were obtained when the operator was pouring petrol into the can and some spilt in the process. Four minutes after the lid had been removed and one minute after it had been replaced the concentration of petrol vapour 3 ft. (91 cm.) from the drum was found to be 2,500 p.p.m.

At first the cause of death seemed debatable. It was suggested that the lad might have been struck by lightning. About the time of his death there had been a thunderstorm; however, the evidence seemed to be that the storm did not reach the area until after his death. There were no burns such as might be found on a body that had been struck by lightning. The excoriation of the skin was due, it is believed, to clothing soaked in petrol, which may cause severe blistering unless the clothing is quickly removed and the skin well washed. Presumably the process went

on after death. There is some evidence that the skin lesions may have been caused by T.E.L. in the petrol (Ministry of Supply, 1950). When leaded petrol evaporates about half of it evaporates before any of the lead comes off. Absorption is rapid through the lungs and unbroken skin. It is stated that T.E.L. has a specific toxic effect on the central nervous system. Death may occur within 10 minutes of exposure to a heavy concentration. A degree of consciousness and sensation is said to persist almost to the time of death.

Fifteen deaths from this cause are recorded by Bini and Bollea (1947). It seems, however, difficult to determine whether these deaths were due to petrol vapour or T.E.L. Cassells and Dodds (1946) describe chronic poisoning from T.E.L. but mention no acute cases. Machle (1941) states that T.E.L. is not a factor in acute poisoning. The possibility of vasovagal inhibition had to be considered, but there was no evidence of any painful stimulus. Nor was there any evidence of pressure on the carotid body or evidence to support such a questionable diagnosis as status lymphaticus or of death occurring in an epileptic fit.

The pathological changes found at necropsy are not specific in death from petrol vapour. If death is not immediate the lesions may be due to the irritant and lipolytic action of the vapour. There may be damage to the lungs, hyperaemia, petechial haemorrhages, subpleural extravasations, and sometimes gross haemorrhage into the lungs. Bronchitis and pleural effusions may be present. Severe acute exposure will cause sudden collapse; death may follow without loss of consciousness. In view of the great concentrations of petrol vapour, well over lethal level, that were demonstrated when the accident was reconstructed, there seems to be no doubt about the cause of death.

Summary

A case of accidental death due to inhalation of petrol vapour is described; the surprising rarity of this kind of accident is mentioned and the post-mortem findings are recorded. The reconstruction of the tragedy is described, showing that the concentration of petrol vapour must have been at a highly dangerous level. The literature is reviewed.

I thank Mr. D. E. Woods and Mr. A. J. Taylor for the estimation of the vapour concentration obtained at the reconstruction of the accident.

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A grant of £50,000 has been made by the King Edward's Hospital Fund for London to assist the North-east Metropolitan Regional Hospital Board in their plans for developing St. Clement's Hospital, Bow, as a modern psychiatric hospital. The hospital already provides to some degree for the mentally sick, in that it has an observation ward and a small unit for psychoneurotic cases. The board consider that in future this hospital will no longer be needed to play any part in providing for the general hospital needs of the area. They have therefore decided to extend the psychiatric work undertaken there, with a view to establishing a modern neuropsychiatric centre for East London. The aim is to provide full facilities for the investigation and treatment of all types of acute mental illness, as well as providing teaching and research facilities.

Medical Memorandum

Spontaneous Rupture of Haematocolpos

Atresia of the hymen is a comparatively uncommon condition and receives but brief mention in most gynaecological textbooks. The possibility of spontaneous rupture of the occluding membrane is not considered in any of the standard works of reference; the following case is described in which this very rare occurrence was encountered.

CASE REPORT

The patient, a girl aged 13, was admitted to hospital on April 30, 1957, because of severe vaginal haemorrhage. Since January she had suffered from attacks of acute urinary retention at approximately monthly intervals, but these had apparently settled readily after the administration of a simple diuretic mixture. Accompanying these episodes there had been some complaint of backache and abdominal pain and a feeling of general malaise. On the evening of admission she had suddenly begun to bleed profusely from the vagina.

On examination her face was pale, but the mucosae were well coloured and there was no evidence of shock. She was afebrile, with a pulse rate of 100 and a normal blood pressure. Inspection of the perineum revealed a bluish swelling just posterior to the urethral orifice; this swelling occupied the normal site of the vaginal introitus and from it a small quantity of dark blood was trickling. Closer examination confirmed that the vagina was occluded by a membrane in which there was a tear, about 3 mm. in diameter, immediately proximal to its anterior border.

Under general anaesthesia the membrane was incised in a cruciform manner, releasing a moderate amount of retained blood. The vagina was greatly distended, the cervix being just palpable at the limit of digital examination. Following operation she was given a course of oxytetracycline extending over five days. Her progress was uneventful, and on May 7 she was re-examined under an anaesthetic before being discharged. By this time the vagina had contracted to a size approximating to normal and the uterus could be easily palpated bimanually; it did not appear to be enlarged. In the pouch of Douglas a moderate quantity of soft clot could be felt, but, as she was symptom-free, no attempt was made to evacuate this. She was allowed home the following day, and has remained well since that date.

COMMENT

The preoperative diagnosis in this case might have been suggested by the history of recurrent attacks of urinary retention, but the picture was complicated by the unusually early age of onset and by the ready relief of symptoms on administration of a diuretic mixture. It is generally accepted that the retention of menstrual blood in cases of haematocolpos is almost invariably due to a membrane situated above the true hymen (Bourne, 1955). Spontaneous rupture of this membrane must be excessively rare, and the only previous reference to this occurrence appears to be an article by Puech (1878) entitled "Imperforation de l'hymen; accidents dépendant de la rétention des menstrues se terminant au bout de dix-huit mois par la rupture spontanée de l'obstacle." In the present case there had been no history of trauma, and it seems likely that rupture was due simply to the effect of increasing intravaginal tension on an abnormally thin area of the obstructing membrane.

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Reviews

POLYMYOSITIS

Polymyositis. By John N. Walton, M.D., M.R.C.P., and Raymond D. Adams, M.D. (Pp. 270+x; illustrated. 32s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1958.

During the last ten years renewed attention has been given to disorders of the voluntary muscles, and the authors of this monograph—Dr. Walton at the Royal Victoria Infirmary, Newcastle upon Tyne, and Dr. Adams at the Massachusetts General Hospital, Boston—have both made important contributions in this field. Although the name "polymyositis" was introduced in 1863 by Wagner, comparatively little interest has been taken in the condition till recently, and, apart from florid cases of dermatomyositis, the diagnosis has only rarely been made. This monograph is based on 40 patients, 25 of whom have been examined by one or other author, the remainder coming from the case-records of the Massachusetts General Hospital; in all of them muscle biopsy specimens were available. The cases in the series vary considerably in their clinical characteristics and to some extent in their pathological features, but the authors consider that in most there is "a single basic disease process related to the other collagen diseases." There is an excellent review of the relevant literature as well as a good clinical analysis, but the outstanding chapter is on the pathology as shown by muscle biopsy. Interpretation of muscle pathology is difficult and often open to more than one conclusion, but this chapter makes the authors' findings quite clear, and the reproduction of photomicrographs, some in colour, is of the highest quality. It seems likely that in the next few years the clinical, pathological, and electrical characteristics of polymyositis will become clearly defined, and possibly even the aetiology discovered. If this should be so, it will be partly the result of this monograph, which is highly recommended to anyone interested in disorders of muscle.

J. W. ALDREN TURNER.

DUSTS, SMOKES, AND MISTS

Particulate Clouds: Dusts, Smoke and Mists: Their Physics and Physical Chemistry and Industrial and Environmental Aspects. By H. L. Green, M.A.(Cantab.), F.Inst.P., and W. R. Lane, B.Sc.(Birm.), F.Inst.P. (Pp. 425+xix; illustrated. 70s.) London: E. and F. N. Spon, Ltd. 1957.

This book comes from the Physics Section of the Chemical Defence Experimental Establishment at Porton, where so much classic work on particulate clouds has been done, and by virtue of its parentage alone the volume would command respect. Part I is concerned with the basic physics and physical chemistry of suspended particles, special attention being paid to the genesis and examination of dusts, smokes, and mists. In Part II theoretical principles are applied to environmental and industrial problems. No clinician can be wholly unconcerned about the nature of aerosols, since many substances of known or suspected physiological action are dispersed in this form. Bacteria, pollens, radioactive substances, tobacco tars, air pollutants, industrial dusts and fumes, agricultural chemicals, and many therapeutic agents may be suspended in the air, and the properties of such systems are fully discussed. The lucid style of the authors is never abandoned in the face of the complexity of their subject. The foreword contains a timely warning against repetitive work and pointless publication, and in the light of this expressed opinion the extensive bibliography—the chapter on health hazards is followed by 126 references—may be regarded as authoritative.

To attempt in these columns to assess the stature of this work as a textbook of applied physics would be an impertinence. The authors say that they have endeavoured to systematize their subject and "bring to it some coherence where only distantly related topics appear to exist," and in the admirable fulfilment of this modest claim they have made, incidentally, a valuable contribution to the literature of clinical science.

P. J. LAWTHER.

EFFECTS OF RADIATION

Medical Radiation Biology. By Friedrich Ellinger, M.D. (Pp. 945+xxxiv; illustrated. £7 10s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

The results of the Japanese atomic explosions and further developments in the warlike and peaceful uses of atomic energy have invested radiation effects with a new importance, and clinicians in most branches of medicine must now be expected to have some knowledge of radiobiology if they are to be able to exercise an informed judgment on problems in which the effects of radiation may play a part. Not only physicians, but also dermatologists, ophthalmologists, haematologists, and others are encountering these problems with increasing frequency, and the need has been felt for a comprehensive work on radiation effects, their mode of production and clinical diagnosis. The present volume has been designed to meet this need, and it may be said at once that it succeeds well in doing so. It covers the whole field of radiation effects on cells and on living tissues, in health and disease, as they appertain to man.

When a subject of this extent and complexity is compressed within the confines of a single volume, from the pen, moreover, of a single author, it is only to be expected that there will be some variation in the coverage of the different aspects of the subject. Thus the sections on fundamental radiation biology are sometimes more in the nature of a summary than of a complete discussion, while those on the effects on human tissues and organs are, generally speaking, full and detailed. The chapters on the effects of ionizing radiations on the skin and its appendages are outstanding. Of special importance at the present time are the chapters on the biological effects of ionizing radiation originating from sources within the body (such as ingested radium and radiostrontium) and that on ionizing radiation as a health hazard. There is an extensive bibliography comprising no fewer than 5,000 references covering the literature up to 1955.

Written as it is primarily for the clinician this is an important and valuable book, and in spite of its high cost in this country it should find a place on the bookshelf of every physician and of those others who may have to deal frequently with problems of radiation effects.

W. M. LEVITT.

AN UNUSUAL THERAPIST

Recovery from Schizophrenia: The Roland Method. By John Eisele Davis, Sc.D. (Pp. 162+xi. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1957.

This book, which consists mainly of extracts from papers, describes the Roland method of treating chronic schizophrenia. Mr. Roland's qualifications are in physical education. After the war he worked with Dr. Karl Menninger at Topeka, Kansas, and became interested in the application of physical activity to the treatment of "regressed" patients—that is, chronic catatonic schizophrenics. The book is noteworthy for the manner in which it conveys Mr. Roland's enthusiasm—one might say evangelical zeal. We are told that the therapist must feel deep down that his own well-being is in some significant way linked with that of the patient, and hints are given on the handling of the "strong interpersonal relationship" which develops between the patient and the therapist. The therapist, indeed, appears to be actively involved emotionally with the patient, a procedure which would seem to be fraught with risks, especially as the therapist apparently receives no psychiatric training.

The method involves "an intensive, continuous, and sustained programme occupying all the patient's waking hours day after day." It can perhaps be illustrated by describing the initial stages. The patient, who is naked apart from his socks and shorts, lies upon the relaxation table. The therapist, whose voice should be soft, kind, understanding, and demonstrate love and acceptance, says such things as, "I am here to help you," or, "I know you can't talk, but I will help you." He then massages the spine, the neck, the face, saying from time to time, "Relax . . . relax." The patient slowly begins to co-operate. The author gives an example to illustrate the dramatic results which can be achieved. One patient after five weeks' treatment assisted the therapist when he held the patient's arm and patted a piece of clay with it, the therapist meanwhile reciting the nursery rhyme, "Patty cake, patty cake, baker man."

The data on the results of this method are sketchy. The main investigation was the Downey evaluation, by a committee of psychiatrists and psychologists. They comment on "the marked discrepancy between the stated objectives of the programme and the results achieved," and would presumably regard "recovery from schizophrenia" as somewhat hyperbolic. It is well known that hospitalized chronic schizophrenics tend to get "bogged down" in sterotypies of thinking and behaviour, and that their behaviour degenerates so that they become dirty, mute, open masturbators, and so on. This is a tendency which has to be combated according to the methods developed by Bleuler and his school. If this deterioration in behaviour has not been combated, any physician who pays attention to these patients will achieve improvements in behaviour, often to a startling degree. It is probably by virtue of this rather than any specificity of his method that Mr. Roland achieves his results. The patient certainly does receive a great deal of attention; one therapist, with his "aides," is fully occupied treating three patients.

The book includes a revealing biography of Mr. Roland. We are told that his "Rohrschach [*sic*] tests have shown underneath the surface much anxiety and tension," and "his tendency to overstrive and overintellectualize is largely a compensatory mechanism." He "has good intellectual potentialities," but "intellectual judgment may suffer at times due to the disrupting and disorganizing components in the personality." Biographies such as this are perhaps a useful innovation.

A. W. BEARD.

MEDICINE AND TOWN PLANNING

Medizin und Städtebau: Ein Handbuch für Gesundheitlichen Städtebau. Edited by Paul Vogler and Erich Kühn. Two volumes. (Volume 1: pp. 700+xv; Volume 2: pp. 727+ix; illustrated. D.M.190.) Munich, Berlin, Vienna: Urban and Schwarzenberg. 1957.

This so-called "handbook" on medicine and town planning, edited by Professor Paul Vogler, a distinguished physician, and Professor Kühn, a distinguished architect, consists of two volumes of Teutonic thoroughness that are weighty in both mental and physical senses. The relationship between health and the environment in which we live is no new subject, and this work does not, it is felt, set out to be original—rather to collate all the evidence from all over the world proving the harm that has been done in the past and indicating the potentialities that may be realized in the future.

While the work is of special interest to architects and town-planners, the medical aspects are dealt with in some detail. For example, diseases of childhood, of the upper and lower respiratory tracts, and of old people can have an obvious connexion with environment. Town planning which uses the land artistically and scientifically is seen as a potent ally in the prevention of disease, and authoritative contributors from many countries have been enlisted in order to prove this.

The late Professor John Ryle, when he transferred his energies from clinical medicine to the newer field of social medicine, deplored that medicine, while profiting over the last quarter of a century from modern scientific and technical advances, had in the process fallen out of tune with some fundamental human needs. The partnership between medicine and town planning is a reform such as he would have visualized. Social planning as here advocated echoes his plea that the basic causes of disease should be in the first line of defence, and their conquest would lead to economies which would make possible a National Health Service in fact as well as in name.

Impressive as are these two volumes, one doubts whether the best-intentioned public-health authority would find the time to study all 1,400 pages. Unfortunately, also, as a book of reference it loses some of its value in having no bibliography, which would facilitate a follow-up of many of the subjects discussed. The illustrations, culled from primitive lands to the newest housing schemes of Scandinavia, warrant unqualified praise, and the index is conscientious and helpful. As befits a work dealing with two specialties ordinarily widely separated, a glossary enables specialists in one field to understand the technical language of the other.

Many of the contributors are not known in this country, but to judge by the high reputation of the two English contributors—E. G. S. Eliot, of the Ministry of Housing and Local Government, and Otto Königsberger, of the London School of Tropical Medicine—they are one and all of the first water, and each deals with his particular subject lucidly and in detail.

The work of the editors must have been stupendous. In the face of such a mammoth achievement one hesitates to ask, Was it worth while?

PHILIP ELLMAN.

TRUTH ABOUT CANCER

Cancer and Common Sense. By George Crile, jun., M.D. (Pp. 143. 10s. 6d.) London: Robert Hale Limited. 1957.

For those who really want to know the truth this is an excellent little book. It is very simple and very sensible, but it is, naturally, written primarily for the American public, who are known to be much more knowledgeable about cancer than their British counterpart. It is of interest to learn, therefore, in view of the efforts which are being made in this country at the present time, especially by the B.B.C., to educate the public about disease in general and cancer in particular, that this same education has had some disturbing effects in the United States. Dr. Crile has, it would seem, thought it necessary to write this book in order to dispel "the fear which those responsible for telling the public about cancer have chosen to use as a weapon." It will come as a surprise to most of us in Britain to read that "the American College of Surgeons has been attacking this group [of surgeons] who exploit fear in order to do unnecessary operations and has been driving them out of many hospitals."

Before leaving this book on their waiting-room tables, doctors should ponder well whether the whole truth about cancer, as stated here, should be told. Dr. Crile himself says that "the harsh facts, at the moment they are revealed, may seem unbearable," and indeed a layman will get little comfort, if that is what he is seeking, from many of the pages of this book. He will learn, for instance, that:

"Our present diagnostic tests are totally inadequate to detect internal cancers at a stage when they can often be cured."

"Our efforts in the last twenty years have failed to reduce the death rate from cancer."

"The most important factor in the survival of a patient is the type of cancer that he happens to have."

Maybe this is the sort of thing that an educated man or woman in 1958 ought to be aware of. But one can foresee quite a bit of trouble for doctors if patients cross-examine them on these lines. For doctors this is a first-class book; for patients it is, in our present state of knowledge, probably better not to know the worst.

MICHAEL HARMER.

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FOETAL BLEEDING

Severe anaemia in the baby at birth is most often due to haemolytic disease, in which the diagnosis of rhesus incompatibility is easily made. Severe anaemia developing soon after birth may also be due to external haemorrhage, usually from the bowel or umbilical cord, which can hardly escape notice. It is less widely known, however, that a non-haemolytic anaemia may be present at the time of birth because of haemorrhage during foetal life. This may not have been visible, or, if visible, the blood may have been misinterpreted as a sign of maternal bleeding. Foetal bleeding constitutes a serious emergency which if not immediately recognized is likely to cost the infant his life. Bruce Chown[1] has recently reviewed the circumstances in which the foetus may develop the anaemia of haemorrhage.

Most common is haemorrhage following incision of the placenta during caesarean section. This hazard has been recognized for many years and is greatest when the lower-segment operation is performed for anterior placenta praevia. Various workers have suggested methods of avoiding damage to the placenta during delivery by this route.[2 3] The foetus may also bleed severely *in utero* from rupture of a blood vessel on the foetal aspect of the placenta, so that the resultant anaemia may have been present for some hours before its birth.[4] This catastrophe should be suspected if during labour bright red blood flows suddenly and in quantity from the vagina. Chown[1] considers that the obstetrician must reach and treat the baby within 3½ hours if its life is to be saved. On the other hand, loss of blood from the foetus via the vasa praevia, or into the placenta itself,[5] may be much less severe. If bright red blood trickles from the vagina before or early in the course of labour it should be tested for foetal (alkali-resistant) haemoglobin.[6 7] A strongly positive result is proof that the blood comes from the foetus and is a warning that treatment may be urgently called for.

The need for prompt recognition of post-haemorrhagic anaemia in the newborn cannot be overstressed. Where blood loss has been severe the infant will be pale and shocked, but the onset of respiration is usually spontaneous and the heart rate is rapid.[1] This contrasts with the slow heart rate and the ineffectual gasps of the infant in a state of asphyxia pallida, who is usually covered with meconium. Hepatosplenomegaly and jaundice are absent. The blood volume returns to normal remarkably quickly after massive haemorrhage in the newborn, and serial estimations of the haemoglobin level in the baby's skin-prick blood afford a relatively reliable assessment of the magnitude of the haemorrhage. G. A. Neligan and J. K. Russell[2] regard a haemoglobin level below 90% (13.3 g. per 100 ml.) as an indication for immediate transfusion. In fact, the need may be so urgent that the normal process of blood-grouping must be forgone. Chown[1] wrote: "The blood that can be obtained *most quickly* is the *right* blood. . . ." In most British maternity hospitals group O rhesus-negative blood would be immediately available.

In the circumstances so far considered, the loss of blood from the foetus is observable before or during delivery and may be classified as overt. By contrast, it may be classified as occult when the foetus bleeds across the placenta into the mother's circulation, a situation first postulated in a case reported by A. S. Wiener.[8] Chown[5 9] was the first to prove beyond doubt that a severe non-haemolytic anaemia in the newborn could arise in this way. Two instances of transplacental haemorrhage from the foetus have recently been reported from Dundee by H. B. Goodall and his colleagues.[10] The clinical picture is one of gross pallor, tachycardia, hypotonicity, and weakness at birth. The liver and spleen are not enlarged and respiration is regular. Blood from the cord or the infant shows the microcytic hypochromic picture of haemorrhage of some weeks' duration. The presence of normoblasts in fair numbers excludes congenital hypoplastic anaemia. When a rhesus-negative mother has been immunized against the foetal red cells by previous rhesus-positive pregnancies, the entry into her circulation of foetal blood has been reported to cause a rigor during labour.[5 10]

Proof of transplacental foetal haemorrhage is to be found in the mother's blood, which should be taken for testing as soon after the infant's birth as

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[5] Chown, B., *Amer. J. Obstet. Gynec.*, 1955, **70**, 1298.
[6] Singer, K., Chernoff, A. I., and Singer, L., *Blood*, 1951, **6**, 413.
[7] Jeaven, G. H., Ellis, M., and White, J. C., *Nature (Lond.)*, 1956, **178**, 857.
[8] Wiener, A. S., *Amer. J. Obstet. Gynec.*, 1948, **56**, 717.
[9] Chown, B., *Lancet*, 1954, **1**, 1213.
[10] Goodall, H. B., Graham, F. S., Miller, M. C., and Cameron, C., *J. clin. Path.*, 1958, **11**, 251.
[11] Bergstedt, J., *Acta paediat. (Uppsala)*, 1957, **46**, 201.

possible. Direct serological proof may be obtained by differential agglutination.[5 9 10] This entails extensive grouping of the bloods of both mother and infant in the hope of finding some antigenic differences which will allow small numbers of the baby's cells to be recognized in the mother's circulation. The maternal blood is incubated with serum containing the appropriate antibodies in saline and in albumin, and the indirect Coombs test is performed. With both techniques the maternal blood will show scattered clumps of agglutinated foetal cells in a background of many unagglutinated maternal cells. Strongly presumptive evidence was obtained in one case by detecting the adsorption of anti-D by a rhesus-negative mother's blood containing D-positive cells from the foetus. Moreover, this mother was shown, after delivery of the foetus, to develop antibodies against D with a positive indirect Coombs test.[9] Goodall and colleagues[10] obtained support for the concept of foeto-maternal transfusion in their two cases by examination of the buffy coat in the mother's blood. In one, who had previously given birth to two infants with haemolytic disease, evidence of the entry into her circulation of incompatible foetal blood was found in the presence of marked erythrophagocytosis. In the other, not previously sensitized to the rhesus factor and not herself anaemic, the buffy coat contained many small ring-stained erythrocytes and tiny normoblasts similar to those seen in her infant's blood and presumed to have come from this source. Direct chemical evidence of transplacental bleeding may also be obtained from the estimation of the alkali-resistant haemoglobin in the mother's blood by a quantitative technique. A gross increase in foetal haemoglobin in the maternal blood is proof of foeto-maternal bleeding, but a level just above that found in normal controls is only suggestive unless supported by morphological and serological evidence.

Finally, mention should be made of another form of occult foetal haemorrhage, in which one twin bleeds through the placenta into the other.[11] In consequence, one twin is born with anaemia which may be severe enough to require transfusion, whereas the other is polycythaemic and may in fact have to have blood removed.

AMERICAN DOUBTS ABOUT B.C.G.

Of the few trials of B.C.G. vaccine on groups of the general population, four have been outstanding. The first is that of J. D. and C. F. Aronson in North American Indians with low standards of living and high tuberculosis rates.[1] About 1,500 tuberculin-negative subjects, from infancy to 20 years old, were given B.C.G. and a similar number left unvaccinated; the tuberculosis morbidity, judged by annual radiography, was studied for 11 years and the mortality for 20 years.[2] The protection against death from tuberculosis was good, about 80%, though, since very few deaths had occurred towards the end of the observation period, it was difficult to be sure that this was maintained beyond the first 10 years. The non-tuberculous death rate was similar in the two groups. The second notable trial is that proceeding under a committee of the Medical Research Council in which 56,000 volunteer schoolchildren, aged 14½–15, in three English urban areas were *x*-rayed and tuberculin tested; those with negative reactions to 100 tuberculin units (T.U.) were given B.C.G. vaccine (14,100), vole bacillus vaccine (6,400), or were left unvaccinated (13,200). The follow-up is by postal and personal contact, annual chest radiography, and ascertainment of clinical cases routinely diagnosed through the National Health Service. The first progress report[3] covered 2½ years and gave an annual incidence of tuberculosis of 1.9 per 1,000 among the unvaccinated, and 0.4 both in the B.C.G. and in the vole-bacillus-vaccinated groups—that is, about 80% protection. There has been no waning of protection by either vaccine up to at least 4 years.[4 5] No death from tuberculosis was reported in any group within 2½ years. The third and fourth trials are taking place under the United States Public Health Service in Puerto Rico, where the tuberculosis rates are still very high,[6] and in two adjacent counties in the states of Georgia and Alabama, where the rates are probably lower than in the catchment areas for the British trial.

A report from the U.S. Public Health Service covering a follow-up period of 6–7 years is now available,[7] the authors being Carroll E. Palmer, L. W. Shaw, and G. W. Comstock. In Puerto Rico nearly 200,000 volunteers aged 1 to 18 were enrolled and tuberculin tested; those negative to 10 T.U. were given B.C.G. vaccine (50,600) or were left unvaccinated either because they refused vaccination (31,600) or through the process of random selection (27,300). Those vaccinated and the controls received an additional test of 100 T.U. In Georgia and Alabama about 64,000 volunteers aged 5 and upwards were *x*-rayed and tuberculin tested; those negative to 5 T.U. were vaccinated (16,900) or left unvaccinated (17,900). The follow-up in both trials is confined to the routine notification of cases to the local health authorities. No periodic re-examinations are undertaken. The most important reason for this omission is now given as the avoidance of bias in the diagnosis of cases, though from an earlier report[8] it seemed that lack of

time, staff, and money were mainly responsible. The calculated incidences of tuberculosis take no account of migration; the true incidences would be underestimated because of this, and also because of using routine notification as the sole method of ascertainment. These factors may indeed provide some explanation for the finding in the Puerto Rico trial that the annual incidence of tuberculosis was only 0.43 per 1,000 among the unvaccinated controls in an environment where 21% of the children entering the trial aged 6 were already reactors to 10 T.U. In the B.C.G. group in Puerto Rico the annual incidence was 0.30—giving a protection by vaccination of 31%, which is statistically significant. For Georgia and Alabama the corresponding rates were 0.22 (controls) and 0.14 (vaccinated) per 1,000—that is, a protection of 36%, which, however, is not statistically significant. The morbidity ratios between controls and vaccinated in each trial had changed little over the period of follow-up.

The effectiveness of B.C.G. vaccination in the non-reactors to the initial tuberculin tests in these two trials by the U.S. Public Health Service is poor compared with the results obtained in the American Indian study and in the Medical Research Council's trial—and indeed runs contrary to previous experience in trials of varying statistical quality in America and elsewhere.[9] [10] Some explanation for this disturbing finding must be sought. Two vaccines from different mycobacterial species—B.C.G. and natural vole bacilli—were used in parallel in the Medical Research Council's trial: in Puerto Rico and in Georgia and Alabama vaccines different from those used in Britain and from each other were used. Did the differences in performance reflect differing post-vaccination tuberculin sensitivities? The American authors point out that, while both vaccines in the British trial produced strong post-vaccinal tuberculin sensitivity and gave good protection, the inferior protection observed in the two American trials was given by one vaccine producing sensitivity of the same high order as in the M.R.C. study and by another with mediocre powers of sensitization—although this in its turn was about the same as in Aronson's successful vaccinations made many years previously. Hence, on the conventional view that the protective efficacy of a vaccine is related to its average sensitizing potency—a theory based on animal experiments[11] [12]—the poor results in the American trials cannot easily be ascribed to low-potency vaccines. On the other hand, this explanation cannot be entirely excluded, since it is possible experimentally to sensitize without protection and vice versa.[13] [14] To have known the proportions of subjects with local vaccination lesions would have provided a useful check, but these were not systematically ascertained. Viable counts of the vaccines would be even more valuable if they were available. If the cause of the American results should indeed be deficient antigenicity it would emphasize the urgency of improving the means of accurately differentiating a good from a less good vaccine. The tests on mice described by G. P. and A. S. Youmans[15] might serve as a useful addition to the usual animal tests of protection. It is worth noting that freeze-dried B.C.G. vaccine has recently been accepted by the Ministry of Health[16] for optional general use in Britain on the basis of its sensitizing potency in man.[17]

Discussing other possible causes for their results, Palmer and his colleagues mention what they consider to be statistical faults in the Medical Research Council's trial; but of the two trials the British would appear to be the more carefully conceived and executed—a true model, according to one authority.[18] For example, no attempt was made in the Puerto Rico study to verify the accuracy of the notifications of disease or death. However, the general high quality of both American and British trials makes it difficult to see how the differences in the degree of protection afforded to the vaccinated groups can be attributed to statistical shortcomings, and there will no doubt be general agreement with Palmer and his colleagues that other reasons are probably responsible. Apart from differences in the vaccines, differences in the populations might have led to divergent results. In the British trial, reactors to 100 T.U. but not to 3 T.U. were excluded from the random selection of those to be vaccinated, and their separate follow-up showed a lower incidence of tuberculosis than among those who were negative to 100 T.U.—though not so low as the incidence among the vaccinated. This may have been due to natural protection. In the American trials vaccination was on the basis of a negative reaction to 5 or 10 T.U., and

[1] Aronson, J. D., and Aronson, C. F., *J. Amer. med. Ass.*, 1952, **149**, 334.
[2] —— —— and Taylor, H. C., *Arch. intern. Med.*, 1958, **101**, 881.
[3] *Brit. med. J.*, 1956, **1**, 413.
[4] Hart, P. D'Arcy, Pollock, T. M., and Sutherland, I., *Fortschr. Tuberk.-Forsch.*, 1957, **8**, 171.
[5] ——*Living Conditions and Health*, 1957, **1**, 159.
[6] *Bull. nat. Tuberc. Ass.*, 1958, **44**, 47.
[7] Palmer, C. E., Shaw, L. W., and Comstock, G. W., *Amer. Rev. Tuberc.*, 1958, **77**, 877.
[8] —— —— ibid., 1953, **68**, 462.
[9] Dahlström, G., *Acta paediat. (Uppsala)*, 1954, **43**, 25.
[10] Rosenthal, S. R., *BCG Vaccine against Tuberculosis*, p. 258, 1957, Boston.
[11] U.S. Public Health Service, *Amer. J. Hyg.*, 1955, **62**, 185.
[12] Meyer, S. N., *Tubercle (Lond.)*, 1956, **37**, 11.
[13] Raffel, S., *Experientia (Basel)*, 1950, **6**, 410.
[14] Weiss, D. W., *Amer. Rev. Tuberc.*, 1958, **77**, 719.
[15] Youmans, G. P., and Youmans, A. S., *J. Immunol.*, 1957, **78**, 318.
[16] Ministry of Health, 1958, Circular 7/58.
[17] Medical Research Council, *Brit. med. J.*, 1958, **1**, 79.
[18] Wallgren, A. J., *Amer. Rev. Tuberc.*, 1957, **76**, 715.
[19] Pollock, T. M., *Brit. med. J.*, 1957, **2**, 20.
[20] Dubos, R. J., *et al.*, *Amer. Rev. Tuberc.*, 1957, **78**, 726.
[21] *J. Amer. med. Ass.*, 1957, **164**, 951.

because there was a particularly high regional prevalence of persons reacting to 100 T.U. only, large numbers of these must have been included in both vaccinated and control groups. This inclusion of persons already partially protected might have reduced the contrast in the incidence of tuberculosis between these two groups. Palmer and his colleagues discuss this possible explanation but are unable to come to a firm conclusion on its authenticity. They have not considered another possibility: could it be that a booster to B.C.G. by natural tuberculous superinfection is required to maintain full effectiveness, and that this superinfection is less common under the conditions of the American than of the British trial, because of a lower prevalence of infectious cases in the communities concerned?

The authors of the American report are at one with the Medical Research Council's workers in recognizing the importance of the yield of cases of tuberculosis from the non-vaccinated group of tuberculin-positive reactors. Estimates of the benefits of vaccination in a community must take note of the proportion of positive reactors to tuberculin and of the estimated future incidence of tuberculosis among them as well as of the infection rate and estimated incidence among the negative reactors, vaccinated and non-vaccinated. Chiefly owing to the 30% effectiveness of vaccination in the negative reactors in the American trials, in contrast to the British 80%, Palmer and his colleagues estimate that only 10% of the total number of cases of tuberculosis in their study populations could have been prevented by vaccination, compared with the estimate of more than 40% over a shorter period of follow-up in the British trial. On this basis, and for other reasons, the American authors believe that in most circumstances in the U.S.A. to-day the disadvantages of B.C.G. vaccination as a means of controlling tuberculosis outweigh its advantages. This generalization may be correct, for infection rates in the U.S.A. are low. But to the further argument that B.C.G. cannot help those already infected it could be answered that earlier vaccination might forestall this,[19] though Palmer would doubtless reply that in his hands effective vaccination has not been evident at any age. His views on the use of B.C.G. in the U.S.A. coincide more or less with those of a distinguished advisory committee of his own service under the chairmanship of Dr. E. R. Long,[20] but differ sharply from those expressed by another equally distinguished advisory committee with Dr. G. P. Youmans[21] as chairman. Whatever the reason for the differences between the results of the American and British trials, the usefulness of the current British scheme for the B.C.G. vaccination of 13-year-old children need not be doubted, at least while morbidity from tuberculosis retains its current importance.

PULMONARY ALVEOLAR PROTEINOSIS

From the U.S.A. comes news that another clinico-pathological entity has been split off from the ill-defined group of chronic diffuse pulmonary infiltrations. In the last five years three distinguished pathologists[1] have collected twenty-seven cases of a disease which "consists of the filling of the alveoli by a PAS-positive proteinaceous material, rich in lipid. This material appears to be produced by the lining cells, which slough into the lumen, ultimately becoming necrotic and yielding granules and variable laminated bodies to the alveolar content." The constancy of the histological structure and the high lipid content of the affected alveoli were remarkable, and only after laborious microbiological, chemical, and spectrographic studies were the authors forced to the conclusion that "pulmonary alveolar proteinosis" represented a distinct entity.

Of the twenty-seven patients, sixteen were studied at the Armed Forces Institute of Pathology. Their ages ranged from 2 to 57, only two being under the age of 19; of the civilians, fifteen were males and six females. Although almost one-half had a premonitory pneumonia-like illness, the exact time of onset could not be determined in the majority. The principal symptoms were slowly progressive dyspnoea, cough, and sputum; when the disease progressed, lassitude and loss of weight were usually apparent. The radiological features, upon which the diagnosis ordinarily rested in the first instance, were strikingly uniform and consisted of a "fine, diffuse, perihilar, radiating, feathery or vaguely nodular, soft density, resembling in its butterfly distribution the pattern seen in severe pulmonary oedema." Since the first patient was diagnosed less than five years ago, the clinical course of this chronic disease cannot yet be fully described, but on the evidence available serial radiographs have shown that eight had improved, thirteen had persistent infiltrations of varying intensity, and eight had died with signs of progressive dyspnoea and cyanosis. Studies of the morbid anatomy were based mainly on biopsy specimens, which showed nodules of yellowish-grey material up to 2 cm. in diameter, from which a milky, pus-like substance oozed on gentle pressure. Necropsy material from seven cases revealed large masses of confluent consolidation.

The problems posed by this newly described disease are manifold. Having been detected in a laboratory, the pathological aspects have received the greatest attention so far. At first, a fungal aetiology was suspected, but exhaustive researches have been unrewarding. The interstitial plasmocytic pneumonia attributed to infection by *Pneumocystis carinii* has been considered in great detail, but numerous staining techniques have failed to show any cysts; the cellular structure is different and the lipid content of the foci is even greater

[1] Roser, S. H., Castleman, B., and Liebow, A. A., *New Engl. J. Med.*, 1958, **258**, 1123.

than in that disease. No bacterium or virus has been incriminated, nor have chemical analyses revealed any causative agent; no excess of beryllium, cadmium, nickel, zinc, or mercury was found on spectrographic examination. From the clinical viewpoint the occupational histories may be significant—four patients worked in or about timber works; two were in the vicinity of broken fluorescent tubes, but no beryllium was found in subsequent tissue analysis; and several were in contact with the newer industrial products such as volatile solvents, plastics, aerosols, and detergents. This range of experience might be expected in an industrial nation, but the cases derived from all parts of the United States, and, of the twenty-seven under review, one each was discovered in Canada, England, and Italy. Whatever the causative agent may be, whether living or inanimate, careful microbiological, chemical, and epidemiological studies must be undertaken, for the disease seems not to be rare. As the lesions appear to be limited to the lungs and possibly the draining lymph nodes, they may well derive from inhaled material, and the possibility that they are a non-specific response to a variety of agents is worth bearing in mind.

This most stimulating paper is bound to cause much interest. The suggested title is somewhat unwieldy in its present form. Perhaps the word "pulmonary" might be omitted, leaving "alveolar proteinosis," which is a big enough mouthful in all conscience, but is probably acceptable to most physicians until more is known of its cause or causes.

PUBLIC HEALTH ON THE ROADS

What is coming to be recognized as one of the great public-health problems of the day[1]—road accidents—was prominent in several different discussions held at the B.M.A. Annual Meeting recently. They caused 5,500 deaths and over 60,000 serious injuries in Great Britain last year. But the attention that these deaths and injuries evoke among medical men is not, unfortunately, to be found among lay people. As Mr. E. J. Dodd, chief constable of Birmingham, said at the meeting,[2] "the sad thing is that road accidents are no longer 'news' and nobody cares about them." And Mr. G. F. Rowbotham saw here the duty of the medical profession to examine and explain this apathy.

Meanwhile a certain amount of technical research goes on into the mechanical causes of accidents, and some of it is outlined in the report issued last week of the Director of Road Research.[3] Owing perhaps to the greater acceleration and smaller wheels of modern cars, skidding is reported to be increasing as a factor in accidents. Figures given for three years show that skidding played a part in 13% of personal-injury accidents in 1954, 14% in 1955, and 15.5% in 1956. Of special interest in the wet summer that we are experiencing is the observation that skidding is more frequent on wet roads in hot weather, so that more skids due to wet roads are seen in summer than winter.[4] But it would seem that at least part of this might be due to the greater impatience of some drivers on congested roads. At any rate, a careful watch is kept for dangerous sites, and the road surface is altered when found to be defective on test. The report refers also to special "on-the-spot" studies of accidents being carried out in Buckinghamshire, Berkshire, and Middlesex. They have given some results of interest. Among them is the finding that car seats are sometimes badly fixed and injuries have been aggravated in consequence. Secondly, a yielding rather than a rigid steering column will reduce the severity of the injury to the driver. Thirdly, toughened safety glass is safer than the laminated variety. And, fourthly, the doors of British cars do not tend to fly open in a smash as do those of American cars.

In relation to the damage done by road accidents the amount spent on research into them—something over £70,000 a year[2]—does seem small, though mechanical safety is probably only a small part of the problem. Many would agree with the speaker who said at the Birmingham Meeting that "inconsiderate, inexperienced, careless, and over-confident motorists are the sinners."

[1] *Brit. med. J.*, 1957, **1**, 753.
[2] Section of Accident Surgery, ibid., 1958, **2**, 305.
[3] *Road Research 1957*, H.M.S.O., 1958.
[4] *Road Research 1956*, H.M.S.O., 1957.

ON TAKING A CUBIT FROM THE STATURE

Society has of late been kinder to tall women. An association ensures that the stores contain the clothes and shoes they need; models, it is said, are taller than they were and some new styles are designed for tall women rather than for short. The Victorian cult of the little woman, whether brave or sweet, has departed. However, most mothers would still prefer that their daughters should not be more than about 5 ft. 10 in. (178 cm.) tall; and if it was possible by medical means to prevent this happening there would undoubtedly be some demand for treatment. On the other hand, there would be little enthusiasm among parents for a treatment destined to prevent boys growing taller than 6 ft. (183 cm.).

Before therapy is undertaken to prevent girls from growing excessively tall two conditions need to be satisfied: first, that ultimate height can be predicted with reasonable accuracy; and, secondly, that such treatment is not harmful. The prediction of ultimate height depends on a consideration of the relation of the present height both to age and to skeletal maturity.[5] The assessment of skeletal maturity is made by *x*-ray examination of epiphyses, and the most accurate methods of doing this have been the subject of much investigation.[6,7] If a girl's height at the age of 12 years is 6 in. (15 cm.) above the 50 percentile, although the skeletal maturity

[5] Bayley, N., and Pinneau, S. R., *J. Pediat.*, 1952, **40**, 423.
[6] Greulich, W. W., and Pyle, S. I., *Atlas of Skeletal Development of the Hand and Wrist*, 1950, Stamford University Press.
[7] Acheson, R. M., *Clin. Orthop.*, 1957, **10**, 19.
[8] Goldzieher, M. A., *J. clin. Endocr.*, 1956, **16**, 249.
[9] Freed, S. C., *J. Amer. med. Ass.*, 1958, **166**, 1322.

is consistent with her age, then an ultimate height of 70 in. (178 cm.) may be predicted. The accuracy of these measurements is subject to many variables, and the forecast has a considerable margin of error. It would therefore be justifiable to give treatment only if the excess above average height promises to be considerable.

Oestrogen, in doses of 2.5 to 5 mg. of conjugated oestrogens daily, has been used[8 9] to reduce ultimate height with apparent success. Its action may depend both on antagonism to the growth hormone (which stimulates linear growth by acting on the epiphysial cartilage) and also by supplying a direct stimulus to epiphysial development. In terms of bone physiology, chondroplasia would thereby be slowed and oestrogenesis would be advanced; linear growth is retarded and ultimate height reduced by more rapid epiphysial development. Oestrogen to produce these effects would have to be given for two or three years, or until the fusion of the epiphyses with the long bones is complete. Uterine haemorrhage may be expected to occur, but the testimony of M. A. Goldzieher[8] and S. C. Freed[9] is that regular menstruation was established in their patients, sometimes before, and always after, therapy was withdrawn. Certainly the evidence seems to be that little permanent harm comes from using the "target" hormones such as oestrogen, testosterone, cortisol, and thyroid. The corresponding anterior pituitary action is temporarily suppressed, but both the pituitary and the target glands appear to recover without damage from their atrophic state, provided it is not too long continued. Conservative endocrinologists and gynaecologists, however, would not recommend that oestrogens should be given to adolescent and pubertal girls to reduce ultimate height without careful consideration of the two conditions here discussed.

MENTALLY HANDICAPPED YOUNG PEOPLE

Three years ago the department of Public Health and Social Medicine at the University of Glasgow produced a useful survey of a group of mentally handicapped girls. A complementary survey on a group of boys has now been completed.[1] Together these surveys trace the history of some 400 boys and girls from the time of leaving special schools for the mentally handicapped in Glasgow until reaching their early twenties. How do they fare?

On the whole their employment record is surprisingly good when the level of intelligence quotient (as estimated at school) exceeds 50 for girls and 60 for boys. About 75% of the girls in this group had a record of at least five years in continuous employment, while only 8 of the boys were unemployed. The girls succeeded rather better than the boys in occupational grade, for about half of them were in semi-skilled jobs compared with only 20% of the boys. However, 13 out of 162 boys had successfully served an apprenticeship and reached the status of skilled craftsmen. Clearly mental handicap is not necessarily incompatible with manual skill. But the picture is not wholly bright. Half of the girls and the majority of the boys were in unskilled, and in many cases unsuitable, jobs. "Often the lads found their way into jobs which were dirty, unpleasant or heavy, or which, from their nature, were not likely to be of universal appeal." One girl in five was found in "general labouring work, often dirty, sometimes in foundries." When I.Q. fell below 60 for boys, or 50 for girls, the record was more often of unemployment.

The marriage rate was about half that for the general population of Glasgow, though when the I.Q. was below 50 the prospects of marriage were more remote. It is much too early to look for information on size of family. A more disquieting feature is the frequency with which the boys run foul of the law. By the age of 22 some 30% had one or more convictions—a rate twice as high as that for a group not suffering mental handicap and for whom figures were available. The pattern showed an increasing rate of delinquency as I.Q. increased. When I.Q. exceeded 70 the proportion convicted exceeded 40%.

Nevertheless the general picture is better than might have been expected. Many of these mentally handicapped young people seem to be leading useful and contented lives. The most difficult problems centre round the virtual unemployability of those with a low I.Q., the ease with which the lesser handicapped are led into crime, and the unsuitability of many of the jobs which the young people accept. Those in the first category will probably always remain a dependent group, but more could be done to help the others. Some local authorities, but by no means all, have set up a special department of their youth employment service to cater for the needs of handicapped children. If this special service were extended, and if industry could be persuaded to co-operate, many of the problems of unsuitable employment might be well on the way to solution. The problem of delinquency is more intractable, and seems likely to remain a serious problem for many years to come. No solution is in sight. Personal supervision has helped in some cases, but the available skilled staff are far too few to make more than a small contribution. The problem must, however, eventually be tackled in a wider context, for a growing body of evidence points to social environment as a major factor. It has frequently been shown that the more depressed areas of our large cities contribute much more than a proportionate share of these unhappy cases. In the legal sphere we are moving towards a doctrine of "diminished responsibility" without waiting for any counterbalancing attack on the social and psychological problems of prevention.

Underlying the whole range of problems is the importance of the home. In the Glasgow surveys, where the home background was assessed as "good" there was a record of less unemployment, higher-grade jobs, and less delinquency. It may be that the best efforts of both central and local authorities, and the whole apparatus of the Welfare State, can provide no adequate substitute for a good home.

[1] Ferguson, T., and Kerr, A. W., *Scot. med. J.*, 1958, **3**, 31.

NUCLEAR WARFARE AND THE TREATMENT OF MASS CASUALTIES*

BY

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The apathy in this country, and perhaps especially among the medical profession, towards Civil Defence and education in protection from nuclear warfare is very evident. One is told either that "it can never happen" or "that nothing can be done about it." Both these statements should be carefully examined.

It is hoped that, in the cause of brevity, some dogmatism will be excused.

Apart from conventional weapons there are three hazards of total warfare—chemical, biological, and nuclear. In the first category, in addition to the well-known blister gases, there is now "G" gas, a colourless, odourless liquid which antagonizes cholinesterase, allowing accumulation of acetylcholine, a few drops causing immediate contraction of the pupil, followed by convulsions and, within four minutes, death. Apart from being under cover or wearing a gas-mask, some protection can be provided by the immediate injection of atropine, 2 mg., and experiments are being made with pyridine aldoxime methiodide (P.A.M.), which may prove more effective.

Biological warfare, which could be so well exploited by saboteurs, has fearful potentialities—incubation periods, mixed infections, and the infection of animals and crops all adding to its danger. Hygiene, knowledge of home nursing, and stockpiling of vaccines and anti-sera seem the only antidotes.

But it is nuclear warfare that perhaps merits most attention—destruction by blast, burns, and radiation liberated by either fission or fusion of the atom.

Mechanism of Nuclear Bombs

The atom bomb (Fig. 1A) consists of two "sub-critical" masses of uranium-235 that can be pressed

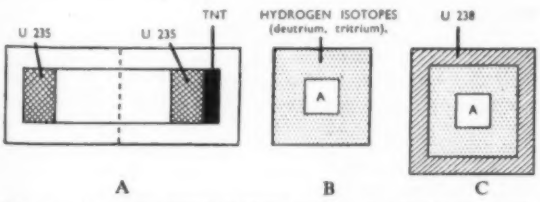


FIG. 1.—A: Atom bomb (fission bomb). B: Hydrogen bomb (fission-fusion bomb). C: Uranium bomb (fission-fusion-fission bomb).

together by a charge of T.N.T., the whole being surrounded by a reflecting tamper. In the "safe" position a shield rests between the two masses of uranium. This is a true fission bomb.

The so-called hydrogen bomb (Fig. 1B), a fission-fusion bomb, is an atom bomb surrounded by hydrogen isotopes which fuse under the influence of the intense heat to form inert helium with release of more energy—a comparatively "clean" bomb if exploded well off the ground.

This bomb can receive yet another coat of uranium-238, which, though less radioactive than the ^{235}U needed for the atom (A) bomb, can be "split" by the large number of neutrons liberated by the hydrogen bomb. The fall-out from this fission-fusion-fission bomb (Fig. 1C) will be radioactive even if no dust is sucked up from the ground and irradiated.

Within minutes of an atom or hydrogen bomb being dropped on the free world, planes would take off with nuclear weapons from hundreds of bases. There would be a few days of holocaust, during which every activity would cease except for attempts to survive, and at the same time to destroy the enemy. After this there would be a long, long period attempting to make the world again a place in which it would be possible to exist.

There are two things that will reduce the risks of such a disaster—being strong, and being prepared for the worst. The latter in particular concerns us, and includes planning for dispersal and the teaching of self-help, first aid, and hygiene. Such preparation, costing nothing, but requiring medical backing, would more than halve the casualty rate—it might in the long run even decimate it. But more of this later.

We have said a word about the mechanism of nuclear bombs, but what of their effect? One "nominal" atomic bomb is equivalent to 20,000 tons of high explosive, more than a quarter of the total tonnage expended on the United Kingdom in five years. One H bomb of 10 megatons is equivalent to 500 times the A bomb or more than 100 times the weight of T.N.T. which fell on this country in the whole war.

Effects

The effect of either the A or the H bomb varies greatly according to the height of the burst, terrain, and weather, but the former would normally be an air burst to obtain maximal blast effect and would then be "clean," with negligible fall-out and with radiation effects only from the flash. The H bomb might well be a ground burst, and, in addition to perhaps some fall-out from an outer casing of ^{238}U, it would draw up in the mushroom cloud behind its fire ball of expanding incandescent gas many tons of dust, in which it would induce radioactivity. The radioactive flash from the H bomb loses its significance, as anything in its area of influence would also be both blasted and burnt to death.

On the burst of a bomb, the sequence would be a fantastic light flash, causing temporary blindness, radiation effects, and intense heat of short duration, igniting material depending on its constitution, colour, and screening. This would be followed by the blast effect many seconds later, allowing time to take cover under a table to seek shelter from glass and rubble. The blast would also fan fires started by the original flash.

With the "nominal" A bomb, the size of that dropped on Hiroshima and Nagasaki, almost total destruction would occur within a radius of ½ mile (0.8 km.), severe blast, burns, and radiation effects for 1 mile (1.6 km.), and houses largely uninhabitable for 2½ miles (4 km.). With the 10-megaton H bomb—on all targets except the large conglomerations of population a 2-megaton bomb might be more realistic—total destruction might be expected over a 3½-mile (5.6-km.) radius, severe damage up to 10 miles (16 km.), and slight damage up to 20 miles (32 km.). With the 2-megaton bomb there would be only slight damage at 10 miles (16 km.). In spite of the "magnifiance" of the H bomb, the A bomb is still likely to be used for military purposes, where ground must later be occupied by the attacker and for some small objectives such as air fields.

Medical Organization

The medical services that must cope with this situation will be civilian augmented by the Services. Broadly speaking, the medical organization will consist of headquarters,

*Presidential address to the Bath, Bristol, and West Somerset Branch of the British Medical Association, 1957.

forward medical aid units, hospitals (acute, auxiliary, and home cover), ambulance-car organization, and medical stores.

The hospital service and mobile units, until called out, will be administered, under the regional senior administrative medical officer, by an area hospital officer, who will be responsible for the direction of casualty admission within his area of some ten thousand beds. The principal medical officer at regional level will advise the Civil Defence Controller.

The first-aid teams, consisting of a medical officer, one S.R.N., and eight or nine auxiliaries, are "mobile"—ready to go to an incident and help to deal with serious emergencies and triage (the sorting of casualties)—or "static," to be situated at each acute hospital and helping to screen it from the less seriously injured cases and, in fact, provide a service for the walking wounded. The mobile first-aid unit is equipped with a car, 10-cwt. (500-kg.) truck, and motor-cycle. Both types of first-aid units are an integral part of the hospital service, but will be assisted as necessary

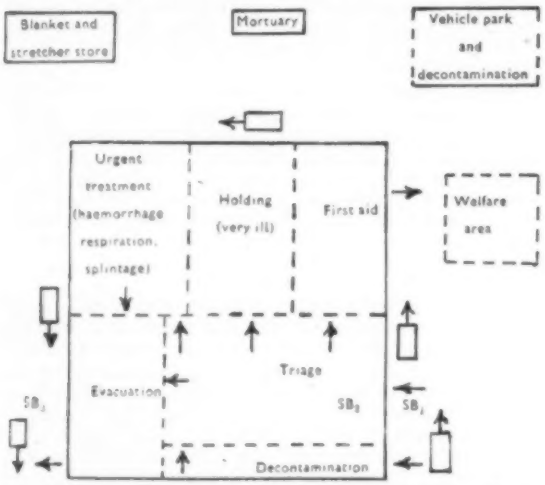


FIG. 2.—Suggested layout of a forward medical aid unit. SB_1 = Squad for off-loading. SB_2 = Squad for internal movement. SB_3 = Squad for on-loading. Triage by team of one senior medical officer, one clerk, and one nursing orderly.

by a casualty-collecting party from the Civil Defence Service. Until called out, both will work in the hospital to which they are attached, and will continue to be maintained by that hospital, but the mobile unit will be at the disposal of the Civil Defence Controller when required.

The tendency is now to group together some four mobile first-aid units to form forward medical aid units of much greater value and potentialities. With these larger units some serious attempt at sorting casualties may be made, and a suggested layout is here given (Fig. 2). On arrival patients would be "frisked," if necessary, with a geiger counter in the ambulance to see whether they need pass through decontamination, to be stripped of their clothes and washed, before entering triage. One or two medical officers of considerable experience should do the actual sorting, each accompanied by one or possibly two clerks and a nursing orderly. One medical officer might superintend both the first-aid section, from which light cases would be passed on to welfare or home, and the holding section for the very sick, though most of the care of the latter would be under the direction of a senior member of the nursing service. Two medical officers will be required in the urgent treatment section, where haemorrhage would be checked and correctable respiratory defects dealt with, and where compound fractures would receive attention. The evacuation section would require only a couple of nursing orderlies. An administrative officer could relieve medical staff of some duties and stretcher-bearers would be in three squads—one for off-loading, one for on-loading, and one situated in a corner of the triage section for internal transportation. Two stretcher-bearers would stand by a stretcher case from its entrance, until it had been taken to first aid, holding, treatment, or evacuation, and they would then return to their rendezvous. Ambulances, after discharging cases, would proceed to an ambulance park, to be cleansed if necessary, pick up new stretchers and blankets, and then await orders.

Documentation must be of the simplest. A casualty label should be attached to the patient, if this has not already been done, with name, main diagnosis, symbols of M for morphine (with dose and time), T for tourniquet (with time), X for priority, H some haemorrhage, and R, C, XX, and P for contamination with radioactivity, blister, nerve gas, or phosphorus. Immediate disposal must be marked on the label in writing or by tabs, and if time is available the patient's address and where he was found should be added. Tabbing could be of five colours: (1) urgent, acute hospital; (2) urgent treatment and then acute hospital; (3) acute hospital not urgent; (4) hold; (5) first-aid and welfare. For the unit record, all that is required is a nominal roll of name, main diagnosis, and disposal.

An "acute hospital" will be any hospital with operating facilities expanded up to its maximum and possibly augmented by the addition of a tented extension provided by the Army. Nursing will be largely by auxiliaries supervised by S.R.N.s. These hospitals will be supported by auxiliary hospitals with approximately an equal number of beds, set up in stores, factory buildings, and the like, under the charge of a general practitioner and relying almost entirely on auxiliary nurses. They will deal with the less seriously ill cases both before and after admission to the acute hospital. In "target areas" only small "home cover" hospitals of not more than 15% normal capacity will be retained to deal with accidents and emergencies, and they will be staffed on a rota basis from one of the acute hospitals in the periphery.

All ambulances and commandeered vehicles for movement of casualties will come under the ambulance and collecting section of the Civil Defence organization. It seems likely that a key point, where a senior ambulance officer should be situated, may be the forward medical aid unit. Here, obtaining reports from ambulances arriving and keeping in the closest contact with the Area Civil Defence Controller, he will be in an excellent position to co-ordinate and control the forward "hauls" and those back to the hospital area.

Medical stores will be stock-piled at strategic points, and it is presumed that they will be under the control of the regional board.

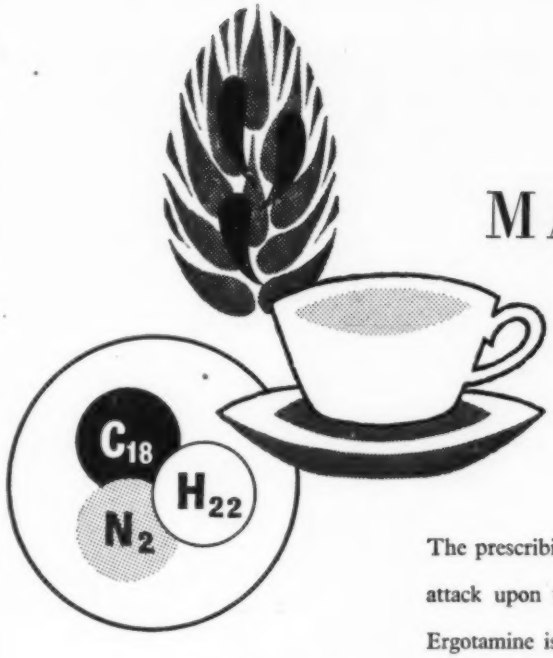
The Army will keep in close liaison with the Civil Defence Authority, and field ambulances, when available, will make ideal forward medical aid units, while military hospitals can open hospital extensions of 200 beds within four hours, if suitably situated.

It is estimated that about 40% of casualties are likely to be due to blast—many caused by flying glass—and that about 60–70% will have suffered some burning. In the later stages radiation casualties will become a problem—perhaps 15 to 30%—but most of these will have to be treated at home.

Sorting

Triage is, of course, of the very first importance. Let us first consider the ideas of forward sorting of casualties and the experience of a large-scale exercise carried out in America in 1956, and then the ideas arising from the United Services Symposium held at the Royal Society of Medicine in June and at the Mayo Clinic in September, 1957 (*Proc. Mayo Clin.*, 1958).

A mobile team with one triage, three resuscitation, and one holding and four surgical sections dealt with 250 "casualties," 90 miles (145 km.) from their base. The "make-up" of the casualties was: major lacerations, 35%; uncomplicated burns, 29%; wounds to the ex-



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1 (*Bufferin in the Management of Rheumatoid Arthritis, J.A.M.A.* 158:386 (*June* 4) 1955.)

2 (*The Neutralization of Gastric Acidity with Basic Aluminium Aminoacetate, J. Pharmacol. and Exper. Therap.* 82:247 (*Nov.*) 1944.)

3 (*In Vitro Differences Between Dihydroxy Aluminium Aminoacetate and Dried Aluminium Hydroxide Gel, J. Am. Pharm. Assoc., Sc. Ed.* 41:361 (*July*) 1952.)

4 (*Effect of Buffering Agents on Absorption of Acetylsalicylic Acid, J. Am. Pharm. Assoc., Sc. Ed.* 39:21 (*Jan.*) 1950.)

5 (*The Pharmacologic Principles of Medical Practice, ed.* 3, *Balto., The Williams & Wilkins Company*, 1954, *p.* 593.)

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tremities, 13%; head and nervous system injuries, 8%; chest and abdominal cases, each 5%; faciomaxillary, 3%; and ophthalmic, 2%. Of the total, 55% had some burning. The planning took 23 days, but as the result of this the units started work full blast within five hours of the alert.

Many lessons were learnt, but in particular the importance of the sorting section, which was staffed by four physicians of great experience. This section was hardly big enough, and it was felt that, with overpowering numbers, many of the hospital sections would have to drop their work and take over sorting and resuscitation. The whole advance station was organized into (1) triage, (2) resuscitation, (3) holding, and (4) evacuation of sections. The motto "The greatest good for the greatest number" had always to be kept in mind. Every effort had to be made not to overload the "acute hospital" section—even with relief teams the number of cases that can be operated on in the first 24 hours is very limited, and General Drummond suggests that a surgeon can operate on only 12 serious cases per day for any prolonged period. Only cases of really top priority must be thus labelled. Head cases did not as a rule merit urgent treatment. All cases were graded into (1) emergency surgery, mainly to check haemorrhage and remove devitalized tissue, (2) resuscitation, and (3) holding (non-urgent, slight injuries, and moribund).

About 50% of cases were sent to the acute hospital, 25% to distant hospitals for less urgent treatment, and 25% kept in the holding unit.

The main lessons learnt from the "exercise" were the importance and magnitude of triage and the need for a very large supply of tracheotomy tubes and blood and blood substitutes. It seemed likely that tracheotomy might very often be required in multiple injuries with C.N.S. involvement and especially when there was the complication of burns.

The Filter Unit

In the recent symposium on the treatment of mass casualties, Colonel Ahern (1957) dealt with triage and the possible use of a filter unit. He envisaged a 10-megaton bomb on a city with a million inhabitants. There might be 210,000 immediate casualties, excluding the dead. Of these, 60,000 would be light cases and 150,000 seriously hurt. Of the latter, 100,000 would be trapped and some be released, dead or alive, within a few days. There would thus be 50,000 untrapped serious casualties to be evacuated to hospitals as soon as possible. This was the debit side of the ledger. On the credit side there were over 50,000 hospital beds at distances of from 5 to 15 miles (8 to 24 km.) from the edge of the devastated area—just enough to care for the untrapped serious cases, but not enough for the trapped cases to follow. A filter unit might consist of 10 doctors, 120 nursing personnel, and 160 stretcher-bearers and "police"—that is, one field ambulance plus a company of infantry. It could filter 6,000 cases in 24 hours (allowing two minutes per patient for sorting and nine minutes for emergency surgery). It is estimated that 40% would be minor injuries, 20% urgent cases, 20% requiring delayed expert treatment, and 20% "write-offs"—labelled expectant treatment.

The unit would first turn away, after first aid, all walking wounded to a Civil Defence Welfare Centre. The remainder, after being monitored, and if necessary cleansed, would pass to the sorting department, and would then be divided into almost equal groups for immediate treatment, evacuation, and holding. This unit should therefore divert from the neighbouring acute hospitals approximately two-thirds of the cases that found their way to the sorting department.

On arrival at hospital, General Drummond (1957) suggests direct admission to the ward of cases filtered elsewhere—in this way 100 patients can be bedded down in 60 minutes. He stresses the hopelessness of overloading a hospital beyond the capabilities of its staff, and recommends the "locking of the gates" when it is full. One medical company can, however, open and admit an additional 100 patients within two hours of arriving at a hospital to which it may be attached. If, however, casualties have not been already sorted, this must be carried out in as large a hall as possible at, or adjacent to, the hospital. In the first instance, with minimal documentation, casualties must be sorted by experts into (1) fit to go home at once or after first aid, (2) for transfer to an auxiliary hospital, (3) cases requiring admission and treatment "at leisure," (4) cases requiring urgent treatment and resuscitation, and (5) moribund.

The serious but treatable cases to be admitted to an acute hospital fall into two categories: the very urgent—easily accessible haemorrhage, correctable respiratory distress, crush injuries of limbs, and open fractures—and the less urgent—15 to 40% surface burns, major closed fractures, and damage to the central nervous system.

Types of Casualty

All who dealt with casualties in the last war will be familiar with the danger of flying glass. Much can be done in prevention by screening and sandbagging windows and taking cover. Only the most severely injured would be able to be admitted to acute hospitals. There would be no scope for professional individualism.

Burns would be on an unprecedented scale, and again only for those where expert treatment is necessary to save life and where life can probably be saved will transfusions and infusions be available—they would largely be reserved for 15 to 40% surface burns, perhaps one-third of the cases. For the remainder, sedation—sodium phenobarbitone, 3 gr. (0.2 g.)—analgesics, copious saline by the mouth, and possibly oral antibiotics and a clean covering for the wounds, will be all that is likely to be possible. Exposure to air with the burnt part raised is, however, perhaps best if practicable. The value of early amputation of a badly burnt limb must not be forgotten. Treatment for anaemia later must also be remembered.

An interesting "help yourself canteen" for the treatment of the less serious burns cases is envisaged by Hunt (1957). Instead of a bun, the customer would collect the appropriate burns dressing; for a drink there would be saline and bicarbonate of soda; and at the cash desk would be some simple printed instructions.

For abdominal casualties, treatment of shock and minimal disturbance before urgent surgery are indicated. Intravenous infusion, gastric suction, antibiotics, and sedation will probably, however, be required. Chest cases may need closure of sucking wounds, release of tension pneumothorax, aspiration from the pleural cavity, maintenance of airway, fixation of a floating chest, and, of course, infusions, oxygen administration, and antibiotics. Lower-limb fractures may indicate skeletal traction by insertion of a Steinmann pin under local analgesia through the tibial tuberosity or os calcis. For the upper limb temporary splintage is all that is required, with no attempt to reduce displacement until later. Waterson (1957) outlines the principle of treatment of fractures by the application of standard plasters, none of which surround the limb or can obstruct the circulation, and which can be put on immediately by pairs of trained orderlies as soon as the medical officer has made the diagnosis.

Radiation Treatment

In the treatment of radiation casualties a selection will have to be made of those most deserving of expert help. Prognosis is therefore the first essential. Some guide to the amount of radiation a person has absorbed can be obtained from calculation of the intensity of radiation, duration of exposure, distance from radioactive particles, and screening factors. Screening and distance factors are illustrated by the fact that 6 in. (15 cm.) of concrete quarters the dose, occupation of the centre ground-floor room of a two-storied house reduces the dosage factor by 40, and staying in a cellar by as much as 300. Intensity of radiation from fall-out at first decreases rapidly, so that an area showing a reading of 1,000 r per hour, one hour after an explosion, will have that reading reduced to 100 r per hour

in 8 hours, to 10 r per hour in 48 hours, and to 1 r per hour in three months. It must be noted that the drop in radiation is much slower in the later stages because this latter radiation is due to isotopes with much longer half-lives. 50 r in 48 hours is considered a permissible dose for rescue workers in an emergency. 100 r will produce some morbidity, 200 r 50% casualties but little if any mortality, and 400 r 50% mortality.

Prognosis on these physical factors is, however, both difficult and uncertain, as some people can absorb nearly twice as much radiation as others without serious harm. The very old and very young are the most susceptible. Pathological examinations would not only be largely impracticable but of little use. We come eventually to old-fashioned clinical medicine and observation, and particularly to timing of onset of symptoms after exposure, for our real guide. If there are no symptoms for 24 hours after exposure and then they consist only of slight vomiting and nausea, the prognosis is good. If persistent vomiting occurs within two hours (a victim may be sick because of shock or other causes), fever before seven days, or purpura or loss of hair before three weeks, the prognosis is probably hopeless. Treatment consists of rest and sedation and a bland nourishing diet with plenty of fluids. In the more severe cases intravenous fluids and antibiotics of the erythromycin wide-spectrum type, to be started after the fifth day, when the leucopenia becomes manifest, may be helpful if available.

The distribution of medical and all rescue planning will have to be governed by "fall-out." As stated before, when a nuclear explosion takes place on or near the ground a large quantity of dust is sucked up and irradiated. This will be carried by the prevailing air currents at the levels it traverses and will gradually settle again down-wind. Meteorological observations will give some indication of likely areas of fall-out, but a zone some 50 miles (80 km.) across and perhaps 200 miles (320 km.) long may be expected. Weather conditions will also determine how long a warning there may be before the fall-out settles—in some areas there may be perhaps an hour. The intensity will be at once plotted and zones demarcated on this information. The policy in the whole area must be to "go to ground," and the critical time for moving again is 48 hours. The reason for this is, as mentioned before, that the degree of radioactivity falls off rapidly for about this time and then much more slowly, and that this time is about as long as it is considered feasible to keep the population under cover. After this two-day lapse, in the periphery the population may be allowed out about half the day, a little more central for two hours, and in the centre, where there is still more than 10 r per hour radioactivity, everyone must be evacuated—but again not till 48 hours after the burst.

Conclusions

What do we learn of practical importance from these sketchy remarks?

Firstly, plans must be made in advance for dispersal of population and voluntary partial evacuation by families in target areas. As the warning period is likely to be short, previous planning is essential. As part of this evacuation, about 80% of all patients would be sent home from all hospitals and the hospitals in the target areas would be completely cleared.

Secondly, enrolment, organization, and teaching of auxiliary nurses is of paramount importance, as on these we shall largely have to rely.

Thirdly, more information must be given to the public on the grounds of reducing panic. The unknown is the worst of all, and besides this there is some reassuring information that can be given. For instance, when a nuclear bomb has dropped it is unlikely that there will ever be another in that area; that flash blindness is often temporary though lasting hours; that mild face burns may cause loss of vision due to oedema for 24 to 48 hours only.

Fourthly, the "stay put" policy must be completely accepted; not only will evacuation after an incident increase risk to the individual from fall-out but it will hamper rescue, and also there may be nowhere for the evacuee to go. A badly bombed but just habitable house is better than none at all.

Fifthly, the population as a whole must learn some first-aid, home nursing, and self-help. Not only will there be no medical services available to deal with the minor casualties, but for those in a fall-out area no help can be obtained from outside for the first two days.

Finally, everyone should know something of hygiene. With concentrated populations in "safe" areas, burst water and sewage systems, and reduced resistance, resulting perhaps from both malnutrition and radiation effects, the results of epidemics might be worse even than the immediate bomb burst. As rigid a standard of hygiene as possible would be essential. Here again the Army Medical Services, with their vast experience, will be invaluable.

I should like to express my thanks to the D.G.A.M.S., Lieutenant-General Sir Alexander Drummond, and to General Lethbridge, Civil Defence Controller of the South-western Region, for reading this paper and for valuable comments, and to officers of the South-western Regional Hospital Board for encouragement and help.

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ADAPTATION TO STRESS

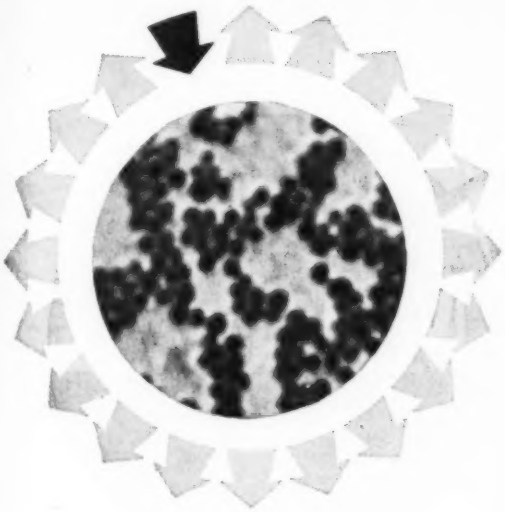
CONFERENCE OF BEHAVIOURAL SCIENTISTS

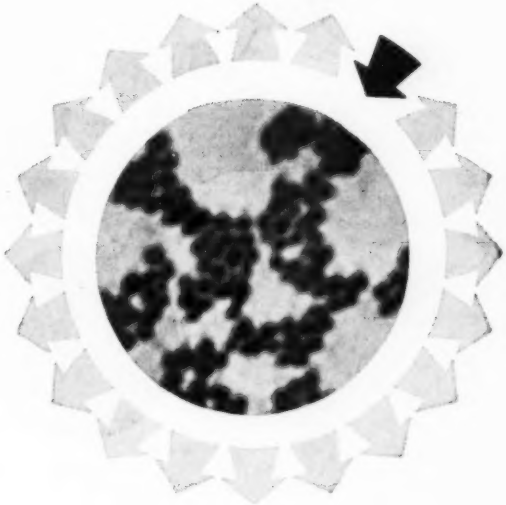
[FROM A SPECIAL CORRESPONDENT]

The Mental Health Research Fund held a conference on "Research on Stress in Relation to Mental Health and Mental Illness" from July 15 to 18 at Lincoln College, Oxford. Its purpose was to arrive at a synthesis of the concepts used in different branches of the behavioural sciences when discussing stressful situations and stress effects, or at least to clarify the differences between the ways these terms are used. Physiology, endocrinology, biochemistry, ethology, psychology, and psychiatry each had one or more representatives, and the conference brought together some 40 scientists, American, Canadian, and British, under the chairmanship of Sir GEOFFREY VICKERS, V.C., the chairman of the Fund's research committee.

Finding a Common Language

The fare was rich and varied. It was hardly surprising, therefore, that, suffering from indigestion, some participants should have expressed doubts about the feasibility and even the desirability of achieving a useful degree of synthesis. They tended then to argue that each branch of science requires to work out its own conceptual models, and that models worked out in other branches lose their precision and usefulness if they are incautiously extended. However, there were few who were not in sympathy with the thesis, argued cogently by Professor R. W. GERARD, of the Neuropsychiatric Institute, Ann Arbor, in a final summing-up, that the behavioural sciences form a unity, and that the processes of adaptation, whether to the physical, biological, or interpersonal environment, have a great deal in common; the similarities are more impressive than the differences. Several speakers had asserted that psychosocial stressors are very different from biological stressors because their meaning and therefore their effects depend upon past experience, which differs from one individual to another. Professor Gerard countered their arguments by pointing out that biological individuality is no less evident than psychological individu-





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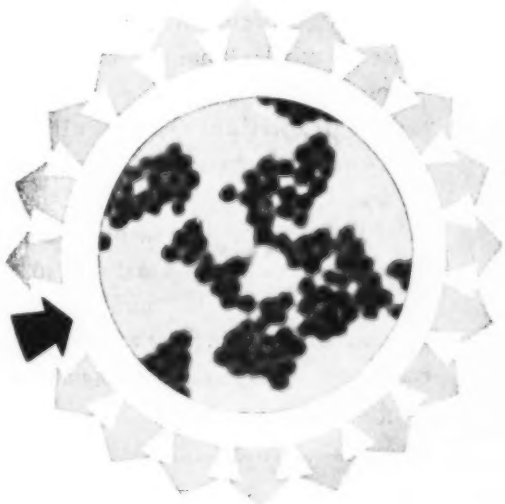

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ality and depends as much upon residues of past experience, remote as well as recent, and that in any event if there were only individuality and idiosyncrasy there would be no science, for the purpose of science is to show what is common to a number of individual instances.

The variety of meanings given to the term "stress" was a source of difficulty in the earlier sessions, for it was used to describe not only factors in the physical, biological, or social environment but also the disorders they produce. The conference soon discovered that confusion could be avoided by speaking of stressors or stressor agents, following Professor HANS SELYE (Montreal University), or stressful situations, on the one hand, or stress effects, stress processes, or distress on the other. Alternatively, the difficulty could be avoided by speaking of a defence reaction, for instance, instead of a stress response.

Restraint and Bereavement

The stressful situations whose effects were discussed were various. Professor SELYE described the effects of immobilization on cats in terms of adrenocortical mechanisms and the general adaptation syndrome. Dr. H. HOAGLAND, of the Worcester Foundation for Experimental Biology, discussed the effects of situations allowing no outlets for aggression on the excretion of adrenaline, noradrenaline, aldosterone, and related compounds by sportsmen, patients, and others. Professor H. S. LIDDELL (Behaviour Farm Laboratory, Cornell University) discussed the part played by restraint in the Pavlov harness and frame in the production of experimental neurosis in pigs, sheep, and goats. Dr. E. J. ANTHONY (Institute of Psychiatry, London) reported on the part played by restrictive and coercive attitudes of mothers in the production of sleep disturbance and encopresis in children. These situations have in common that the organism is restrained or confined, and the restraint prevents or imposes delay on adaptation. Superficially, although perhaps not fundamentally, they differ from the other psychosocial stressors discussed.

Professor E. LINDEMANN, of Harvard University Medical School, described the effects on the health of adults of bereavement—that is, what he termed "the cessation of interaction with an emotionally relevant person." Professor M. ROTH (Durham University) reported similar effects in the elderly, and Dr. JOHN BOWLBY (Tavistock Clinic, London) pointed out the similarities in the concept of bereavement and his own concept of the effects on the young child of separation from the mother. Brigadier R. PHILLIPSON, director of Army psychiatry, reported on the effects reflected in official sickness statistics of removing young men from their families for the two-year period of National Service. Mr. E. L. TRIST (Tavistock Institute of Human Relations, London) discussed the effects of the reorganization of working groups on the sickness-absence, accident-rates, and productivity of coal-face workers. Professor H. G. WOLFF, of the New York Hospital, reported data which show that disturbances in social relationships perceived by individuals as threatening are correlated with increases in the incidence of a wide range of diseases, many of them not hitherto regarded as "psychosomatic" (such as bronchial carcinoma). Professor LIDDELL reported that kids which have been separated from their dams for an hour or two immediately after birth suffer a very high mortality subsequently, the majority dying within a year. All these psychosocial stressors demand from the individual a "role transition" and a reorganization of social relationships, which may be successfully accomplished; otherwise illness and even death result.

Conflict and Monotony

This does not exhaust the list of stressful situations discussed. Dr. R. A. HINDE (Cambridge University) described the several different classes of behaviour observed in birds when they are subjected to conflicting stimuli to behave in incompatible ways or when they suffer deprivation. Professor LIDDELL told how the presence of the mother reduces the effects on lambs of monotonous, unreinforced stimulation. Lambs so tested in the presence of their mothers move freely and actively about the pen; lambs separated from their mothers become virtually immobile.

The attempt was made by several speakers to identify the common features in all these situations. Stressful situations, it was remarked, are those in which drives remain unsatisfied, or expectations are not fulfilled; there is a mismatch between the actual and the target (the "is" and the "ought-to-be"), business is unfinished, problems are not resolved, or there is a crisis—that is, suspense in the taking of a decision. Perhaps all these definitions amount to much the same thing.

The stress-strain analogy from physics is unsatisfactory in at least one important respect, it was agreed, when the effects of stress on organisms are considered. The effects constituting strain in materials cease as soon as the stress ceases, whereas the agents or situations which cause strain in the adaptation mechanisms, even if they produce disorganization, tend also to produce reorganization, which is not reversed. Great importance was attached by several speakers to the processes of reorganization, whether they described these as "reprogramming," "the establishment of new defences," or "the redistribution of interactional patterns"—for example, following bereavement. Dr. DENIS HILL (Institute of Psychiatry, London), in an interim summing up, defined stress as a "process of change during which a new adaptation may be reached."

Fixity of Response Under Stress

There appears to be a general tendency for the reorganizations which result from stress to involve a narrowing, or stenosis, in the range of activities of the organism. A striking instance of such restriction in activities and interests is seen in the traumatic neuroses, and especially in the selective forgetting, or repression, which may follow upon stress. Reorganization in a given case may be evaluated by reference to the number and range of factors which the subject is able to take into account in making decisions. It is worth noting that each role-transition undergone by human beings as they grow up in a complex society tends to bring with it an increase in the specialization of their skills and interests.

Reorganization represents an at least partially successful adaptation to stress. Before it is accomplished, however, manifold changes in mental activity, behaviour, and physiological functions may be observed which reflect the homoeostatic mechanisms and may be regarded as attempts at adaptation and restoration or reorganization. Psychological observations suggest that stressful situations tend to produce immediately a narrowing of attention, or preoccupation, with a corresponding neglect of things that are peripheral in place or significance. At the same time as perception is thus affected, behaviour tends to become less versatile and more restricted and stereotyped. Another aspect of this tendency is the fixation of responses, which is a characteristic result of stress; particular responses tend to be repeated even after they have proved ineffective in relieving the stress. Thus the effects of stress on behaviour are selective. It is tempting to suppose that the uneven distribution of the effects of stress upon physiological and especially endocrinological functions reflects a similar tendency.

Dr. J. I. LACEY (the Fels Research Institute for the Study of Human Development, Yellow Springs), in particular, emphasized that the strain is always distributed unevenly; there is overaction of some mechanisms and underaction of others. He reported evidence to show that specialization and stereotypy in the responses of the autonomic nervous system to stress occur at least as early as 6 years old—that is, organ-vulnerability is established by this age. He asserted that the differential distribution of the effects shows some consistency over years and is largely independent of the nature of the stress. He attached major importance, therefore, to the constitutional determinants.

Professor SELYE pointed out, however, that the pattern of the stress responses composing the general adaptation syndrome varies widely with the conditions that are established experimentally, and Dr. HOAGLAND'S results also show that the adrenal medulla's pattern of responses depends largely upon the nature of the stressful situation. There is probably some truth in both views.

EAST AFRICAN PHYSICIANS

The following are some of the points brought out at the annual conference of the Association of Physicians of East Africa, which was held in Nairobi from June 26 to 28 under the chairmanship of Dr. A. D. CHARTERS.

Tuberculous pericarditis is common in East Africa, according to Dr. P. P. TURNER, and often fatal. In about a third of the cases he could culture tubercle bacilli from the pericardial fluid. He recommended treatment with antituberculous drugs, prednisone, and intrapericardial hydrocortisone. Although this might save life, the end result was poor and surgery might be needed. Dr. A. A. KHAN described 28 cases of radiologically proved duodenal ulcer in Africans admitted to the King George VI Hospital, Nairobi, between September, 1957, and April, 1958. Statistically, duodenal ulcer was on the rise in Africans in Kenya, and it affected all income, social, and educational groups. Dr. Khan thought it would become yet more frequent as urbanization of the African progressed. Dr. A. G. SHAPER said that steatorrhoea, on the other hand, was excessively rare in Africans. He described two cases.

Dr. J. M. VAIZEY illustrated the change chloramphenicol has made in the outlook for the typhoid patient by comparing the results achieved at Mulago Hospital in 1957 with those in 1949, when chloramphenicol was not available. Mortality had fallen from 24.5 to 7.5%, and the duration of fever and of stay in hospital by about a half. The complications of haemorrhage and perforation still remained serious, however. Dr. Vaizey also reported the emergence of a resistant strain of *Salmonella typhi*. Dr. K. SOMERS described the severe iron-deficiency anaemia which often occurs with heavy hookworm infections in Uganda and sometimes leads to heart failure. He demonstrated the reversible E.C.G. changes found in 15 such patients.

Dr. P. MANSON-BAHR read a paper on histoplasmosis in East Africa. All forms of the disease had been reported there—the localized, the disseminated, and the benign pulmonary form. Dr. Manson-Bahr then described a case of benign pulmonary histoplasmosis (or "cave disease") in a European male who had visited the Amboni caves near Tanga (Tanganyika), where the floor is covered in bat guano. Symptoms developed 14 days later and a histoplasmin skin test was positive. Treatment did not help, but the patient made a gradual spontaneous recovery.

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Apresoline (Ciba Laboratories Ltd.).—This is 1-hydrazinophthalazine hydrochloride, or hydrallazine, in tablets of 25 mg. or ampoules containing 20 mg./ml. Hydrallazine lowers arterial blood pressure by producing generalized vasodilatation. In addition to reduction of blood pressure, cardiac output and renal blood flow are increased. The glomerular filtration rate remains unchanged or falls as a result of glomerular arteriolar dilatation. After intravenous injection, the arterial pressure begins to fall within 20 minutes, reaches its lowest level between 20 and 90 minutes, and returns slowly to pre-injections level in 4–8 hours. The cardiogram may show transient ST depression and T wave inversion, especially in subjects with hypertensive or ischaemic heart disease, probably as a result of increase in cardiac output without increase in coronary artery flow.

Hydrallazine can also reduce arterial pressure when given by mouth, but side-effects may be prominent, consisting of headache, flushing, palpitations, oedema, nausea, and vomiting. In about 10% of subjects a syndrome resembling systemic lupus erythematosus appears after 4–8 weeks' treatment and necessitates withdrawal of the drug.

The side-effects of the drug limit its value, while the effect on cardiac output prohibits its use in patients with hypertensive or ischaemic heart disease. It is usually less satisfactory than the ganglion-blocking agents, but has been used in combination with hexamethonium or reserpine. It may occasionally have a place in the treatment of patients with hypertension and renal failure in whom the reduction in renal blood flow produced by ganglion-blocking agents is undesirable. It is advisable to start treatment with small doses and increase gradually. In late pregnancy, the free passage of ganglion-blocking agents across the placenta may cause dangerous ganglion blockade in the foetus, and in these circumstances a limited course of hydrallazine by mouth, or in emergency by injection, may be warranted if reduction in blood pressure is required.

N.H.S. basic price: 100 25-mg. tabs., 11s.; 100 50-mg. tabs., 20s. 4d.; 6 ampoules, 10s.

Predsol Nasal Drops (Glaxo Laboratories Ltd.).—Prednisolone disodium phosphate 0.1% in isotonic buffered solution.

Predsol-N Nasal Spray (Glaxo Laboratories Ltd.).—Prednisolone disodium phosphate 0.025%, neomycin sulphate 0.5%, and naphazoline nitrate 0.025% in aqueous solution.

Delta-Feno Nasal Spray (Boots Pure Drug Co., Ltd.).—Prednisolone 0.01%, phenylephrine hydrochloride 0.25%, naphazoline nitrate 0.025% in an aqueous solution.

This is a series of preparations of prednisolone for local application to the nose for hay-fever and vasomotor rhinitis. Provided the presence of serious infective conditions such as sinusitis can be excluded, there seems no objection to their use. They provide an alternative to hydrocortisone snuffs, and seem to be equally satisfactory and rather easier to use. Predsol, which contains only prednisolone, would seem likely to be the most satisfactory preparation, but no doubt the combination with neomycin is unobjectionable for local application to an infected allergic mucosa.

N.H.S. basic price: Predsol nasal drops, 10 ml., 5s.; predsol-N nasal spray, 15 ml., 5s.; delta-feno nasal spray, 15 ml., 3s.

Hibitane Dihydrochloride (Imperial Chemical Industries Ltd.).—This compound, chlorhexidine dihydrochloride, is a slightly soluble white powder which is strongly bactericidal against a wide range of micro-organisms, including staphylococci, streptococci, and coliform bacilli. It can be sterilized by dry heat at 150° C. for one hour. Resistant strains are not found and do not emerge in attempts at habituation. Its activity is somewhat diminished by contact with serum and blood.

Because of its bactericidal properties and low solubility, chlorhexidine dihydrochloride has been found suitable and safe as an application to burns, with some prophylactic action especially against *Staph. aureus*. It is desirable to use it in combination with other agents, such as neomycin and polymyxin. The cream should be made with a non-ionic emulsifying wax (e.g., cetomacrogol *B.P.C.*) and contain 1 or 2 mg. "hibitane" dihydrochloride per gramme of cream. It is unlikely to be of therapeutic benefit in cases of established infection. Wound-dusting powders (5% with lactose) have also been used. For other uses of chlorhexidine, such as disinfection of skin and of instruments, the soluble chlorhexidine diacetate is more suitable.

N.H.S. basic price: 10 g., 7s.

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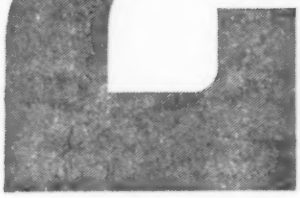

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Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Tabo-paresis

SIR,—Some senior and experienced psychiatrists have recently had cause to give considerable thought to the topic of tabo-paresis. One British psychiatrist recently found that there was concern in responsible circles in America on the same topic. When the time-lag between primary infection with syphilis and the onset of tabo-paresis is considered, it appears possible that the recent virtual disappearance of tabo-paresis is due to the efficiency of arsenical treatment in the years before the large-scale employment of antibiotics.

It may be that cases treated in the early years of the antibiotic era have yet to develop tabo-paresis. The time factor suggests that the next few years may be particularly important in this respect. Recently a senior psychiatrist with considerable experience of neurosyphilis had four cases referred to him within a very short period—more cases than he had seen for a very long time previously. Two of these cases could easily have been missed by a more junior man with little practical experience of tabo-paresis. Moreover, some of the old, characteristic physical signs seem to be changing somewhat.

It may be hoped that fears of a reappearance of tabo-paresis on a considerable scale may prove groundless, but there appears to be reason for clinicians to be very alert on this topic, so that if an increase in the number of cases should occur the sufferers from it may be diagnosed early and therefore successfully treated.—I am, etc.,

NOEL G. HARRIS,
Chairman, Public Relations Committee, Royal Medico-Psychological Association.

London, W.1

Neurological Complications of Pertussis Immunization

SIR,—Drs. D. C. Thursby-Pelham and C. Giles's letter (*Journal*, July 26, p. 246) is of great interest. It is remarkable that Dr. Thursby-Pelham has seen six patients in the space of 10 years with neurological reactions following pertussis immunization, in view of the fact that only seven such cases have been recorded in Great Britain (see my paper, *Journal*, July 5, p. 24). One of these seven is Case 2 in their series. It may be, as Drs. Thursby-Pelham and Giles state, that the dangers of whooping-cough immunization are greater than is commonly thought, but this can only be established if the possibility of reactions to immunization are borne in mind and reported when they occur. One would like to make a plea, therefore, that this should be done.

It is possible that the relatively large number of cases of neurological complications of pertussis immunization reported from the United States, as opposed to other countries, including Britain, is due to a greater awareness of, and interest in, the problem in America. If further cases are reported, as Drs. Thursby-Pelham and Giles have now done, it may be that the commonly held view, that the dangers from whooping-cough itself are much greater than those from immunizing against it, will require modification.—I am, etc.,

J. M. BERG.

London, S.W.17.

SIR,—Further to the article by Dr. J. M. Berg (*Journal*, July 5, p. 24) and the letter from Dr. D. C. Thursby-Pelham and Dr. C. Giles (*Journal*, July 26, p. 246), I have given many thousands of injections of both combined diphtheria–pertussis and triple antigen vaccines, and in two instances only have I known convulsions to follow, in sisters.

Case No. 1.—A female infant, first child of a Rhesus-negative mother. Became jaundiced three days after birth. Was admitted to hospital but replacement transfusion unnecessary. At 6 months of age she had a severe convulsion which occurred four hours after her first injection of triple antigen. She was unconscious for 10 minutes and made a full recovery within 24 hours. One month later she had a similar convulsion following her second injection. The third dose was not given and one year later she was seen and is quite normal.

Case No. 2.—Sister of Case No. 1. Female infant. Second child of a Rhesus-negative mother. Labour was induced at 38 weeks. At birth, the infant was severely affected by haemolytic disease and replacement transfusion was carried out. At 4 months of age the first injection of triple antigen was given. Three hours later a minor convulsion occurred. Recovery was complete within a short while. In view of her sister's reaction after her second injection, and after reading the article by Dr. Berg, no further injections were attempted.

The fact that these two cases were sisters both suffering at birth from haemolytic disease and both born of a Rhesus-negative mother makes me wonder if the aetiology of this dangerous reaction to pertussis vaccine may not in some way be connected with the Rhesus factor.—I am, etc.,

JOHN N. H. ANDREWS.

Tetbury, Glos.

Dummy Tablets

SIR,—Dr. E. C. Atkinson (*Journal*, June 21, p. 1478) makes out a case for having "some control tablets of inert substances" or "a genuine placebo" included in the *British National Formulary* to help doctors with their investigation of "the relative values of the mass of proprietary drugs" which appear on the market. Dr. W. N. Leak (*Journal*, June 28, p. 1546) points to the difficulty which may arise for a doctor prescribing dummy tablets, when he has to choose between honesty with his patient and impersonal science; and concludes "regretfully, that it would be wrong for the *B.N.F.* to include a dummy tablet. . . ." May I set out in detail some of the considerations which should guide a family doctor in his choice of controls for any therapeutic research which he intends to pursue?

It is not primarily the task of a family doctor to test the pharmacological effects of unknown or untested substances on those who seek his advice about their treatment. Logically a doctor could only advise a patient to take such an unknown substance if there was no accredited or orthodox treatment for the condition from which he was suffering. The medicaments prescribed by a general practitioner should be those which he uses in good faith and on the basis of knowledge which he has obtained of their composition and action from different sources. Where the progress of a disease invariably follows a predictable and well-established course, then the past experience of accumulated medical knowledge supplies the control for any therapeutic trial of a possibly beneficial drug, and no other may be needed. The most obvious examples are those diseases in which death is the invariable or predictable result. If, on the grounds of a reasonable hypothesis, the first therapeutic trial of a new substance for the treatment of such a disease were being planned—for example, streptomycin in tuberculous meningitis—it could be argued that it would be unethical to withhold this test substance from *any* patient in the trial. A proper structure of this first trial might well be to test the action of the new substance in a continuous series of cases until the question was beyond doubt, either that it had no action or that the predictable course of the disease was undoubtedly altered by the use of the test substance. In general practice, however, such trials are rare.

Therapeutic research in general practice falls broadly into six categories. The first, and perhaps a neglected field, is a fresh assessment of the action of time-honoured remedies in common diseases—for example, the use of potassium iodide or tincture of stramonium in asthma. Second comes the controlled trial of new drugs for old and familiar diseases, such as the prophylactic use of sulphonamides for the complications of measles. Third come trials designed to reveal new uses of familiar drugs, such as aspirin in diabetes. Fourth, and we hope rarely in general practice, comes the administration of new and unfamiliar drugs to patients with diseases for which a standard treatment already exists. The fifth comprises those trials where the family doctor is in ignorance of the precise nature of the

substance which he personally prescribes or dispenses for any particular patient—for example, "blind" trials—and, lastly, there is the experimental use of drugs in volunteers who may be either sick or healthy.

In planning a therapeutic trial of any of the first three types, if a control is necessary, what kind should be selected in general practice? There are four possibilities: (i) the action of the drug in question may be compared with that of one or more other accredited remedies already in common use for that particular disability (e.g., potassium iodide or tincture of stramonium in asthma; sulpha drugs or penicillin in measles); (ii) the action of the test substance may be compared with that of one or more *innocuous* substances or mixtures, whose accepted use in general practice lies as much in their psychological as in their chemical value, in so far as they have been found to allay any apprehension by the patient that nothing could be done for his condition (placebo); (iii) the action of the test substance may be compared with that of one or more "inert" substances; strictly speaking these should have been proved already to have absolutely no positive or negative action on the course of the disability for which they are given, but more commonly the phrase is used to include substances which are *expected to be inert* but whose action in this disability has never been put to a critical therapeutic trial. Where an "inert" substance is made to resemble in presentation the form of the test substance, the use of the phrase "dummy" tablet (mixture, capsule, etc.) is not only justified but more explicit, since it draws attention to the purpose of the counterfeit, which is to deceive the patient and often also the doctor taking part. (iv) The action of giving the test substance may be compared with that of withholding it. In fact this is what is done in both (ii) and (iii) above, and the reasons for choosing either (ii) or (iii) rather than (iv), or for choosing (iii) rather than (ii) needs to be examined closely.

In trials of the fourth, fifth, and sixth types mentioned above—namely, with unfamiliar drugs—if the general practitioner is working "blind" or where the consent of the patient is sought, legal and ethical as well as statistical difficulties may arise for the investigator. For example, it is the duty of a doctor to act only in what he considers to be the best interest of each individual patient. He ought not, in relation to any particular patient, to regulate his treatment according to any other consideration unless with the express knowledge and approval of his patient. An "infant" cannot and his parents may not give consent for any treatment not directed towards his own benefit; he may not be experimented on for the sake of others. Furthermore, it is dangerous to rely merely on the knowledge and approval of the patient, because he does not have the necessary medical knowledge to enable him to appreciate in full the considerations involved; the doctor would have to be quite sure that the patient really had a full appreciation of the position. This is particularly important when the toxicity of the trial substance is uncertain or known not to be negligible. Failure to act in accordance with the principles set out above might expose the doctor to risk of legal proceedings, based on a breach of contract or duty, or on assault.

Any general practitioner taking part in the National Health Service has a further duty to carry out his terms of service conscientiously and to the best of his ability. In selecting an inert substance as the only treatment of a patient seeking medical advice, the legal requirements of the terms of service under the N.H.S. would seldom, if ever, be met.

In dealing with new drugs a clear distinction should be drawn between a general practitioner's use of an unfamiliar drug on the advice of a consultant, as the appropriate and necessary remedy for a particular patient, and his use (either alone or with others) of a drug with which he is unfamiliar or uncertain, as part of a clinical trial on patients, whether volunteers or not. It is one thing to use a familiar drug as a new line of treatment in some particular condition; it is quite another to experiment with new drugs on our patients as though they were guinea-pigs.

Finally a word about "blind trials," in which the person observing the response to treatment is intentionally kept in ignorance of whether a particular patient is receiving the trial drug or a control. Such an observer is really acting as an assistant to those who planned the trial. A family doctor who is in general practice as a principal could ethically be in some difficulties about taking part in such a trial, unless he had a share in its design, since he is personally responsible to his patients for the treatment which he prescribes for them. An assistant, however, can act as observer for his principal, and a single-handed practitioner can plan his own "blind" trials, if he in turn seeks help from a nurse or relative as observers, or in appropriate cases from the patient himself. This applies particularly to trials in which treatment is given for the relief of symptoms, such as pain, sleeplessness, worry, or anxiety, rather than for the alteration of physical signs which the doctor himself can observe. For all these reasons I agree with Dr. Leak, without regret, "that it would be wrong for the *B.N.F.* to include a dummy tablet. . . ."—I am, etc.,

Peaslake. G. I. WATSON.

Congenital Dislocation of the Hip

SIR,—In your annotation on congenital dislocation of the hip (*Journal*, July 5, p. 38), you say that most cases of the disease in this country are diagnosed at the age of 1 or 2 years. A recent answer in "Any Questions?" referred to asymmetry of the skin creases as a useful sign.[1] Much earlier diagnosis could and should be made. Professor Marino Ortolani,[2] director of the Instituto Provinciale per l'Infanzia, Ferrar, has described a sign which can be elicited in newborn babies which is obviously not sufficiently well known in this country. First the thigh is flexed on the abdomen; then pressure is exerted along the long axis of the femur. The femur is then abducted. As the head of the femur rolls over the rim of the acetabulum there is a click, which may be felt or even heard.

From now on all newborn babies should be subjected to this manœuvre at their first examination. In this way cases will be detected early, and much suffering prevented.—I am, etc.,

Bath. H. R. E. WALLIS.

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Aetiology of Cancer

SIR,—The highly interesting lecture on the aetiology of cancer by Dr. Ludwik Gross (*Journal*, July 5, p. 1) prompts me to draw some conclusions from the viewpoint of a clinician. The principle of "vertical transmission of potentially pathogenic agents" remaining harmless to their hosts often for generations and activated into cancer-producing pathogens only occasionally by "obscure reasons," "intrinsic or extrinsic stimuli," necessitates the following unavoidable logical conclusion as to human cancer aetiology. The latent harmless pathogenic agent must be ubiquitous in humans, since there is hardly any human family without a case of malignancy in the last four or more generations. In other words, every human being would be potentially susceptible to malignancy and the real enigma of cancer aetiology would remain unsolved because "the obscure reasons" for activation of the cancerogenic virus would be completely unknown in the great majority of human cancers.

We must taken exception to Dr. Gross's statement that genetic factors as contrasted with "vertical transmission" are "transmitted in an orderly and foreseeable manner." This is not the case where polygenic (multifactorial) heredity is involved.[1] As to inheritability of predisposition to malignancy, it can be foreseen as little as physical resemblance of a child *in statu nascendi* to any of his ancestors. Thus the genetic concept of cancer aetiology does not seem to me to be overthrown by the concept of "vertical transmission" of a virus. The question of similarity of a gene with a virus, however, is another matter.—I am, etc.,

Los Angeles, Calif. JULIUS BAUER.

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Childhood Malignancies

SIR,—I have read with great interest the paper of Dr. Alice Stewart and her colleagues entitled "A Survey of Childhood Malignancies" (*Journal*, June 28, p. 1495). If diagnostic *x*-rays can cause leukaemia, it is reasonable to assume that they can also cause non-malignant changes of importance in the leucopoietic tissues. It is known that toxic substances like benzol which can cause leucopenia can also cause leukaemia. It would be interesting to know whether diagnostic *x*-rays can, in childhood, cause leucopenia, however slight, especially after radiographs which have been taken in pregnancy.

The dose concerned in radiodiagnosis is very small, and the radiation which penetrates the bone and reaches the bone marrow is only about 10% of the surface dose. The reticulo-endothelial apparatus on the other hand receives the full surface dose over the entire body. This radiation could easily be significant in a foetus of which a radiograph is taken during pregnancy. According to Dominici,[1] even myeloid cells can originate in the reticulo-endothelial apparatus, as I was able to confirm.[2] Non-malignant changes in the leucopoietic system, caused by *x* rays, are usually eliminated by recovery, but can lead, if permanent leucopenia ensues, to leukaemia or impairment of cellular and humoral reaction.[3,4] In order to avoid the exposure of the entire radio-sensitive foetal reticulo-endothelial apparatus to radiation, radiographs should be avoided during pregnancy, if not strictly indicated.—I am, etc.,

St. Albans. F. FREUND.

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Comfort in the Surgical Ward

SIR,—Your leading article entitled "Comfort in the Surgical Ward" (*Journal*, July 12, p. 95) prompts me to make a few comments and a practical suggestion regarding post-operative thrombo-embolic phenomena. These "complications" still occur in spite of (and as you mention) early ambulation, since the process has commenced *before* the patient has recovered consciousness and is fit to carry out the various exercises, etc., advised. There are other factors—e.g., the indolent patient, changes in the constituents of the blood, etc.

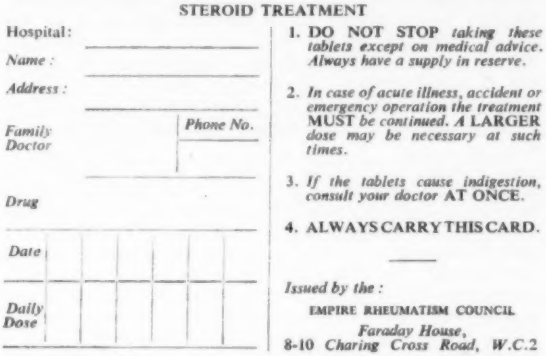
Why is it that the thyrotoxic patient so very rarely suffers thrombosis and embolism? In the few hundred thyrotoxic cases I have operated on I cannot recall a single case of thrombosis or embolism. The absence in the thyrotoxic of these phenomena—so distressing and dangerous—may be due to the faster circulation time, high B.M.R., increased hyperkinetic movements in bed, a lowered blood cholesterol level, etc., all of which should be considered and assessed. This freedom from thrombosis, etc., occurs whether the operation on the thyrotoxic patient is in the neck or in another region. As a practical suggestion I submit that, as a prophylactic, we should make patients somewhat thyrotoxic *before* operation. Here again the risks would have to be considered.—I am, etc.,

Dundee. F. R. BROWN.

Card for Patients on Steroid Therapy

SIR,—It is recognized that sudden withdrawal of steroids in patients undergoing long-term treatment may be dangerous, particularly when such patients have been subjected to sudden stress, such as an acute illness, accident, or emergency operation. In these circumstances it may be of vital importance for the physician or surgeon responsible for the patient's immediate care to be made aware that the patient has been on steroid therapy, the form in which it is being administered, and the daily dose.

The education subcommittee of the Empire Rheumatism Council gave this matter consideration at a recent meeting and reached the conclusion that a useful purpose would be served by the issue of a card (see Fig.) to patients receiving steroids, stating the preparation in use and its daily dose. The hospital or clinic supervising the patient's treatment and the name and telephone number of the family doctor should


STEROID TREATMENT
Hospital:
Name:
Address:
Family Doctor
Phone No.
Drug
Date
Daily Dose
1. DO NOT STOP taking these tablets except on medical advice. Always have a supply in reserve.
2. In case of acute illness, accident or emergency operation the treatment MUST be continued. A LARGER dose may be necessary at such times.
3. If the tablets cause indigestion, consult your doctor AT ONCE.
4. ALWAYS CARRY THIS CARD.
Issued by the:
EMPIRE RHEUMATISM COUNCIL
Faraday House,
8-10 Charing Cross Road, W.C.2

also be recorded along with simple instructions to the patient. I have been instructed by my committee to bring this matter to your notice, as the Empire Rheumatism Council would be prepared to make a supply of these cards available to any physician who might wish to use them.—I am, etc.,

Faraday, House,
8-10, Charing Cross Road,
London, W.C.2.

J. J. R. DUTHIE,
Chairman, Education Subcommittee,
Empire Rheumatism Council.

Post-operative Pulmonary Function

SIR,—In their paper on the effect of abdominal operations on total lung capacity and its subdivisions (*Journal*, July 12, p. 84), Mr. Anthony R. Anscombe and Dr. Roger St. J. Buxton mention that they gave a bronchodilator (aminophylline) to two of their patients before and after partial gastrectomy and found no significant changes in the total lung capacity and its subdivisions. In 1950 I measured the maximum breathing capacity (M.B.C.) pre-operatively and post-operatively before and after the inhalation of 1 ml. of a bronchodilator (isoprenaline) in 12 patients undergoing elective repair of inguinal hernia. It was found that, whilst there was a reduction in M.B.C. after operation, there was no significant increase in the M.B.C. before or after operation after the bronchodilator in patients who had normal chests. In two patients with mild bronchitis, however (one of whom developed atelectasis), although there were trivial increases in the M.B.C. after the isoprenaline pre-operatively, post-operatively after the bronchodilator there were increases of 20% and 30%.

Subsequent experience with a large number of cases confirmed this suggestion that patients with slight and often unrecognized bronchitis are most likely to develop post-operative atelectasis when undergoing abdominal operations. The reason for this is that they readily develop bronchospasm and secrete viscid bronchial mucus, which in combination with the reduction in ventilatory capacity which occurs in all patients to some extent after abdominal operations, leads to sputum retention, atelectasis, and bronchopneumonia. These considerations led to the development of a regimen which was found to be very effective in the prevention and treatment of post-operative atelectasis.[1]—I am, etc.,

Aberdeen. K. N. V. PALMER.

REFERENCE

1. Palmer, K. N. V., and Sellick, B. A., *Lancet*, 1953, **1**, 164.

Dysgerminoma in Pregnancy

SIR,—Dr. Jill M. Evans's report of a case of dysgerminoma in pregnancy (*Journal*, July 12, p. 105) was very interesting, but, without being captious, one may ask why a patient, 14 weeks pregnant, who had a "mobile firm swelling . . . the size of a foetal head," was discharged

from hospital and not subjected to laparotomy until four weeks later. It is surprising that so many textbooks still subscribe to the view that ovarian tumours should not be removed until after the 16th week of pregnancy because of the increased risk of abortion in the earlier months. Under modern conditions, however, the planned removal of pelvic tumours would appear to be far less dangerous to the foetus than the 10 to 20% abortion rates given by McKerron[1] and Spencer,[2] the usual authorities quoted, and any increased tendency to abortion would be more than outweighed by the technical advantages of operating in early pregnancy—ease of access, less handling of the uterus, etc.

In a paper read to the Newcastle Obstetric Society in May, 1954, I reported a series of 46 cases in which ovarian tumours and fibroids had been resected in early pregnancy with only one abortion resulting. (Most of the operations were performed by my former chief, Dr. Frank Burke, of Sunderland.) No fewer than 17 patients were dealt with during the first trimester, and in three of these an active corpus luteum was found in the cyst wall on section. During the past three years I have performed a further two myomectomies and excised five ovarian cysts before the 16th week without any foetal loss. Solid ovarian tumours are apt to be malignant (as in Dr. Evans's case), and by virtue of their weight and mobility there is a greater tendency to torsion. Hence I feel that the preferable policy for such cases is to operate as soon as possible without any reference to the duration of pregnancy.—I am, etc.,

Ballinasloe, Co. Galway. J. P. O'DWYER.

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1 McKerron, R. G., *Pregnancy, Labour, and Childbed with Ovarian Tumour*, 1903. Rebman, London.
2 Spencer, H., *Tumours Complicating Pregnancy, Labour, and the Puerperium*, 1920. Harrison, London.

Chromosomal Sex and Abnormal Sexual Development

SIR,—Since reporting upon an investigation into the oral smear method for the determination of chromosomal sex in a group of 260 normal individuals[1] we have had opportunity to apply the technique to more than 60 cases of abnormal physical or psychological sexual development. As was the case with normal individuals, we experienced little difficulty in determining the chromosomal sex from oral smears, and, provided the criteria which were stipulated in the previous study were observed, a count of 25 cells proved sufficient. With the younger cases, the youngest child being 1 month old, the examination was a little more tedious, for, as we also observed previously, it is difficult to find the appropriate number of suitable cells in a single smear. We would advocate therefore in these cases that as routine practice more than one smear should be available for examination.

The results from this further application of the oral smear technique emphasize our earlier contention that in the majority of cases skin biopsy for chromosomal sex determination appears to be unnecessary.

The present series includes cases of true and pseudo-hermaphrodites; Turner's and Klinefelter's syndromes: eunuchoids, transvestites, and homosexuals. The method has been particularly useful in separating out those cases with definite physical abnormalities—for example, Klinefelter's or Turner's syndrome—from those of an essentially psychological nature, without resort to laparotomy. In the psychologically maladjusted group it has been our invariable experience that the physical sex diagnosis is borne out by the chromosomal sex findings.

It has been most interesting to note that the incidence of sex chromatin in some of the chromosomal females with physical abnormalities has been surprisingly low, falling well below the normal incidence range[1]; in a limited number of cases this feature has also been observed in the mother of the patient. However, at this stage we are unable to comment on the significance or otherwise of this finding. Finally we would agree with other workers[2,3] that, whilst this method appears to give a true diagnosis of genetic sex, it should not be allowed to exercise undue influence in the determination of the "social sex" of the individual.

We are much indebted to Professor R. Platt, P.R.C.P., of Manchester Royal Infirmary; Mr. L. R. Broster and Mr. J. Adler, of Charing Cross Hospital; and Drs. P. M. F. Bishop, F. Osmond-Clarke and M. Murray, of Chelsea Hospital for Women, for sending us material for investigation.

—We are, etc., A. D. DIXON.
J. B. D. TORR.

Manchester, 13.

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1 Dixon, A. D., and Torr, J. B. D., *Brit. med. J.*, 1956, **2**, 799.
2 Barr, M. L., *Lancet*, 1956, **1**, 47.
3 Segal, S. J., and Nelson, W. O., *J. clin. Endocr.*, 1957, **17**, 676.

Suffocation in Infancy

SIR,—Dr. W. H. Davison (*Journal*, July 26, p. 248) is quite right to reply to Dr. J. Shackleton Bailey's letter (*Journal*, July 12, p. 104). Our own findings would go even further than those of Dr. Davison's survey in Birmingham. Even when the circumstances would appear to be greatly in favour of overlying, it is frequently possible to find an adequate natural cause of death. We are prepared to go so far as to suggest that the *normal* child is never simply "found dead in bed or cot from external mechanical suffocation."

I feel that it is important for the benefit of other children in the same family when a child is found unexpectedly dead that the parents should not be subjected to a police investigation. It is surely not necessary for a doctor to submit a child immediately to the coroner as a suspected case of suffocation if he can in the meanwhile obtain the parents' consent for necropsy, and have the body examined by a pathologist experienced with such cases. It is equally important that the parents should not be blamed for leaving a child on a pillow or taking it into bed with them.—I am, etc.,

Sheffield, 10. JOHN L. EMERY.

Iron Preparations

SIR,—In Dr. C. F. Herridge's interesting paper on the comparison between ferric chelate and established iron preparations (*Journal*, July 19, p. 140), the question of cost is raised in assessing the choice for a given patient with iron-deficiency anaemia. The preliminary report of the Hinchliffe Committee has made many of us price-conscious, and therefore I have calculated the price of the three iron preparations, adding for comparison the *B.N.F.* mist. ferr. sulph. pro inf.

Dr. Herridge gave his three mixtures for six weeks, and I have calculated the total of each required to give his suggested dose. Some difficulty arose with the new ferric chelate mixture ("sytron"). The daily elemental iron (assuming a utilization factor of 14%) available from the dose he used is somewhat higher than the figure given. However, the commercially available sytron differs from the preparations available for Dr. Herridge's investigation in being only nearly half the strength (380 mg. per 8 ml. (approx. 2 drachms) instead of 600 mg.). I have therefore provided the price of 21 oz. (596 ml.) as suggested by Dr. Herridge, and of 27 oz. (767 ml.) as calculated to produce the daily figure of 142 mg. elemental iron. In the case of mist. ferr. sulph. pro inf. the quantity required to give the same daily amount of elemental iron (using the utilization factor of 14%) is 1.4 oz. (39.4 ml.) per day—a total amount of almost 60 oz. (1,704 ml.) for the six weeks. However,

Drug	Am't	Basic	P.T.	On-cost	C–A	D–F	Total
"Sytron"	27	200	60·5	65·125	1·55	48	375 (31s. 3d.)
	21	155·5	47	50·63	1·55	24	278·7 (23s. 3d.)
"Ferlucon"	10·5	75·5	Nil	18·88	1·55	14	109·93 (9s. 2d.)
"Ferromyn"	8	94	28	30·5	1·55	14	168 (14s.)
Mist. ferr. sulph. pro inf.	60	80	Nil	20	1·55	48	149·55 (12s. 5½d.)
	21	28	"	7	1·55	42	60·55 (5s. 1d.)

Am't: Quantity in fluid ounces (1 oz. = 28 ml.) calculated for six weeks. Basic: Cost of ingredients or wholesale price. P.T.: Purchase tax. On-cost: An additional 25% of the basic price + purchase tax. C–A: Container allowance. D–F: Dispensing fee. Total: in pence.

clinical experience suggests that two drachms twice daily (0.5 oz. (14 ml.) per day, or a total of 21 oz. (596 ml.)), gives a satisfactory haematological response. I have therefore priced both 60 oz. (1,704 ml.) and 21 oz. (596 ml.) of the *B.N.F.* mixture.

The various factors which go into the price paid under the N.H.S. for a drug have been listed separately (in pence, as is the customary method). I find this breakdown of the total cost is as instructive as the cost itself. If any comment is to be made from all these figures it is that, while some preparations may have a valuable place in treating difficult cases (either difficult diseases or difficult patients), as "tonics" or placebos we should be very wary of their price.—I am, etc.,

London, W.12. STUART CARNE.

Heat Illness

SIR,—Among the discoveries of Ur was a little clay image of the "God of the South Wind." Homer[1] mentions the death of one hero, during a battle before Troy, due to a "stroke from the Sun God" (translation by Andrew Lang). Alexander the Great (*O si sic omnia!*) chose the winter for his Mesopotamian campaign, culminating in the battle of Arbela on September 20, 331 B.C., attended by a lunar eclipse.

Your enlightened annotation and the article "A Classification of Heat Illness" (*Journal*, June 28, pp. 1351 and 1353) draw attention to a little-considered but very important problem. Clinically the "effects of heat" are numerous, and most extensively displayed by W. H. Willcox.[2] For practical purposes, hyperthermia (heat stroke) and heat exhaustion (heat collapse) may include all the major disorders; prickly heat and heat cramps being merely symptoms, although very unpleasant ones. The best and most universal form of treatment is the provision of an artificially cooled environment for the sufferers. Modes of prevention include suitable acclimatization, avoidance of drugs like atropine; anaesthetics are also taboo (unless in a cooled theatre); ichthyosis is an absolute bar to employment in the Persian littoral (gathered from bitter experience). For armies that have to consider shipping space a form of "iron lung" with mechanical refrigeration could be used to revive cases in the zone of operations. The Croonian Lectures by Dr. H. L. Marriott[3] reveal a first-hand knowledge of the problems involved. He had to deal with conditions where no mechanical aid was possible: that phase should belong to the past. I have also made suggestions for improvement in hospital and living conditions and for better treatment.[4,5] The writings of the late Professor M. S. Pembrey[6] deal with the investigation of the problems of marching men. Endocrine factors are still much neglected—as remarked in your annotation, but the artificial production of "coolth" is still the keystone of the arch of treatment.—I am, etc.,

Epping, Essex. FRANK MARSH.

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2. *Brit. med. J.*, 1920, **1**, 392.
3. Ibid., 1947, **1**, 245, 285, 328.
4. Marsh, F., *British Encyclopaedia of Medical Practice*, 1937, Vol. 6, p. 396. Butterworth, London.
5. —— *Trans. roy. Soc. trop. Med. Hyg.*, 1930, **24**, 257; 1933, **27**, 255; 1935, **29**, 309.
6. *J. roy. Army med. Cps*, 1913, **21**, 156; 1914, **22**, 692.

Prevention of Lung Cancer

SIR,—Whilst agreeing strongly with the ideas embodied in Dr. Lennox Johnston's letter (*Journal*, June 21, p. 1483) on the need for a national campaign to put the facts about smoking and lung cancer squarely before the public, he does, I think, miss one rather strong point. He omits the importance of directing such a campaign against children and young adults. The middle-aged man who has been smoking all his life is almost beyond redemption, but the children of to-day are the lung-cancer victims of thirty years hence, unless they can be taught the wisdom of not smoking. Young men in the Forces are also accessible to education in this matter; my own Service days were punctuated by lectures and films on the dangers of venereal disease, malaria, and typhoid, so I should think that some education on the dangers of smoking would not be out of place.

Taken in its broadest aspect, the question of smoking and lung cancer has now entered the domain of preventive medicine, and as doctors we are neglecting our precepts and responsibilities if we do not say, "At last here is a positive approach in dealing with one major malignant disease, that of *prevention*." Which medical man in his right mind would fail to be shocked to learn that one of his patients was daily drinking tuberculous milk—particularly if this was a young person? And yet, year in and year out, every doctor has a large number of his patients paving their way to early and unpleasant deaths by a daily habit which is just as preventable as the marketing of tuberculous milk.—I am, etc.,

Boston, Lincs. E. R. NYE.

Cancer Education

SIR,—I am sorry to have to take issue with so eminent a correspondent as Professor Ian Aird, but I feel most strongly that in his letter on cancer education (*Journal*, June 14, p. 1417) he has fallen a victim himself to the "education and propaganda" which he seeks to uphold. The term "cured of cancer" is probably more frequently used on this side of the Atlantic than Professor Aird's, and I am becoming more than ever convinced that its use is as much to satisfy the ego and present methods of the therapeutist—be he surgeon or radiologist—rather than to indicate the true status of the patient. After all, it rather depends on one's standards of "cure." If this only amounts to, say, one year's survival—to take an arbitrary figure—then a so-called cure is relatively easy to obtain, but if, on the other hand, 5, 10, 15, or 20 years of survival is demanded, then a cure becomes correspondingly more difficult to obtain. A cure can only be certain when a patient has received treatment for a carcinoma, and necropsy at some later time demonstrates that death is due to some other cause and that there is no evidence of the original carcinoma either macroscopically or microscopically.

I question the wisdom and truthfulness, in the present state of our knowledge, of instilling in the mind of the general public the idea that sometimes cancer, especially early cancer, is a curable disease. There is absolutely no proof to back up this statement. Absolute survival figures of treatment of carcinoma have altered little over the decades, and what improvement there has been is entirely due to the fact that blood transfusion, chemotherapy, antibiotics, and vastly improved anaesthesia have caused fewer patients to die from the immediate effects of treatment of the primary growth. Relative survival statistics are not worth the paper they are written on, as they are always "loaded" because the operator is choosing the most suitable cases for his particular type of therapy. By "early cancer" is meant a small circumscribed lesion, with no evidence of metastasis and a short or absent history. This could just as easily be an old carcinoma in terms of morphological time but one which is slow growing and slow to metastasize, which is the reason why it has not been picked up earlier. Obviously, treatment of such a lesion would lead to a reasonable survival time, but this is due rather to the nature of the carcinoma than the time at which treatment was given, as the lesion is a slowly growing and slowly metastasizing one.

Cancer detection clinics may have failed to improve the mortality from the disease, but they have contributed a great deal of useful data to our knowledge of the natural history of carcinoma. It now appears likely that a frankly carcinomatous epithelium may be restrained from spreading through the basement membrane and remain *in situ* for a variable time—sometimes for years. The epithelium may regress and return to normal, or it may progress to a frank carcinoma by the carcinomatous cells bursting through the basement membrane. The patient's fate is then decided by the metastasizing ability of the cells, and this occurs at a period of time long before a diagnosis is made. Again it is a question of standards when one discusses early carcinoma, and I do not think I need to labour the point further, except to point out that many doubtful carcinomas are being treated as carcinomas, with consequent vilification of statistics and subjection of patients to unnecessary surgery.

I have no objection to the public receiving cancer education as advocated by Professor Aird, provided it is based on truth, but can this be done at this time? May I draw the attention of your readers who are interested in this subject to two particularly informative and thoughtful articles which have probably been neglected because they do not subscribe to popular orthodox opinion, but which do indicate that perhaps a glimmer of truth is beginning to emerge from the morass in which we find ourselves. I refer to a paper by J. R. S. Douglas[1] entitled "Survival Curves as a Means of Investigating Cancer," and George Crile, junior's, paper "Factors Influencing the Spread of Cancer."[2]—I am, etc.,

Petersburg, Virginia, U.S.A. J. KENWORTHY OGDEN.

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[1] Douglas, J. R. S., *Med. J. Aust.*, 1957, **1**, 536.
[2] Crile, G., jun., *Surg. Gynec. Obstet.*, 1956, **103**, 342.

Chloramphenicol Suspension for Intrathoracic Infections

SIR,—We would like to draw the attention of your readers to our experience with a suspension of 15% chloramphenicol for use as a local application in the treatment of certain intrathoracic infective conditions. We have used the suspension in six cases so far and have been favourably impressed with the results.

The series of six cases comprised five patients with pulmonary tuberculosis and one with a bronchial carcinoma. All six cases had surgical treatment carried out and developed their intrathoracic complications following operation. One of the tuberculous patients had a right upper lobe excision and developed a *Staph. aureus* empyema, and this responded to a course of systemic chloramphenicol combined with daily aspiration of the empyema space and the instillation of the suspension. In the other cases the infecting organism was a *Staph. aureus* too, but because of the nature of their condition and the operation performed it was difficult to eradicate completely the factors favouring continuation of their infection. Two of these were pneumonectomy cases who developed a *Staph. aureus* empyema of the pneumonectomy space, and although the suspension helped temporarily in overcoming the infection there was still a residual space left which would favour the perpetuation of chronic infection.

We feel it justifiable to publish these results, as in one case there was complete cure and in the other five cases definite clinical improvement was obtained. We feel, therefore, that the preparation described has a useful place to play in the local treatment of certain types of intrathoracic infections.

The 15% suspension was kindly supplied to us for clinical trial by Parke, Davis and Co., Ltd., through the kind auspices of Dr. H. W. Pearson

—We are, etc.,

NORMA MCFARLANE.
JOHN M. REID.
JOHN G. STEVENSON.

Newton Mearns, near Glasgow.

Pioneers in India

SIR,—On reading the report of the opening of the Eighth Congress of the Medical Women's International Association (*Journal*, July 26, p. 244), I was surprised that the name of Dame Edith Brown was not mentioned among the pioneers in India. Dame Edith probably was the first woman doctor in India to receive this award. She founded the Women's Christian Medical College in Ludhiana, Punjab, about 1895. I am sure there are many, like me, who appreciated the loyal and trustworthy work done by the graduates of the Women's Christian Medical College, Ludhiana.—I am, etc.,

Cobham, Surrey. HILDA L. KEANE.

Medical War Crimes

SIR,—My letter (*Journal*, July 5, p. 551) seems to have been so badly worded that I appeared to champion Dr. Herta Oberheuser. My intention was otherwise, and I would like to make this quite clear. I wished, in fact, to champion justice, which, I felt, might miscarry if we were ignorant of the facts about her as she is now. This information was not presented.

I did not state that she was a "dedicated practitioner," only that she might be, which is a very different thing. There is not the slightest doubt in my mind about the enormity of her past behaviour, and for this very reason I thought it important to know something about her now. I felt that justice demanded such knowledge and that our verdict should have been tempered by it. However, it is obvious that, when the medical profession sits in judgment on its members, this particular principle is not observed.—I am, etc.,

Chesterfield, Derbyshire. A. P. TAIT.

Orthopaedic Medicine

SIR,—I feel that the review by Professor J. H. Kellgren of the *Textbook of Orthopaedic Medicine* by Dr. James Cyriax (*Journal*, July 12, p. 93) should not be allowed to pass without comment. Some of the observations made are incredible. It is stated that "much of the treatment proposed seems to be of unproven value, since most of the complaints he is dealing with are naturally of short duration." Is it being suggested that a backache lasting several years is a complaint of short duration, and that, when it is dramatically relieved by manipulation, this contributes nothing to the immediate improvement? The sceptics may say that patients helped by manipulation are hysterics or neurotics, but in my opinion that is an admission of failure to explain the result, and every general practitioner knows that it is not a satisfactory explanation.

I do not know what is meant by the statement "the author shows a disregard for the dangers of spinal-cord lesions which have been so clearly demonstrated in recent neurological work and anatomical studies of the cervical spine," but I do know that I have given lasting relief to patients with backache and "fibrositis," by manipulation. I also know, after attending Dr. Cyriax's clinic, that the treatments carried out there are urgently needed in general practice and would result in a saving of thousands of pounds by removing these patients from the physiotherapy department, where they receive general physiotherapy of little or no value.

The material in the *Textbook of Orthopaedic Medicine* is based on years of experience in this work and thousands of cases successfully treated. The opinions given in the review are coloured too much by morbid anatomical studies, and I feel that the importance of careful clinical observation is not fully appreciated.—I am, etc.,

Hemyock, Devon. THOS. LOGAN.

Electrified

SIR,—The other day, starting the septic hand clinic, I reached out to examine the first patient's hand, when, to my surprise and his, as our hands were about one inch (2.5 cm.) apart there was an audible snap. I experienced a sharp needle-like stab of pain in my thumb and the patient a similar stab in his index finger which made us both withdraw our hands involuntarily.

In many thousands of examinations I have never previously received a static electric shock, and so far as I could judge there was nothing peculiar about our clothing or the atmospheric conditions on this occasion. I wonder whether any of your readers have had similar experiences or can throw any light on the occurrence?—I am, etc.,

Birmingham, 4. LIONEL H. PIMM.

POINTS FROM LETTERS

Fidgety Legs

Dr. PERCY G. HARRIS (Belfast) writes: "Orthoxine" (methoxyphenamine) is claimed by the makers as being effective for the relief of nocturnal leg cramp in old age and pregnancy. It occurred to me that patients complaining of "leg fidgets"—that most disturbing syndrome to the unhappy sufferer—might also benefit. In a small series this treatment has proved most effective, being almost 100% successful.

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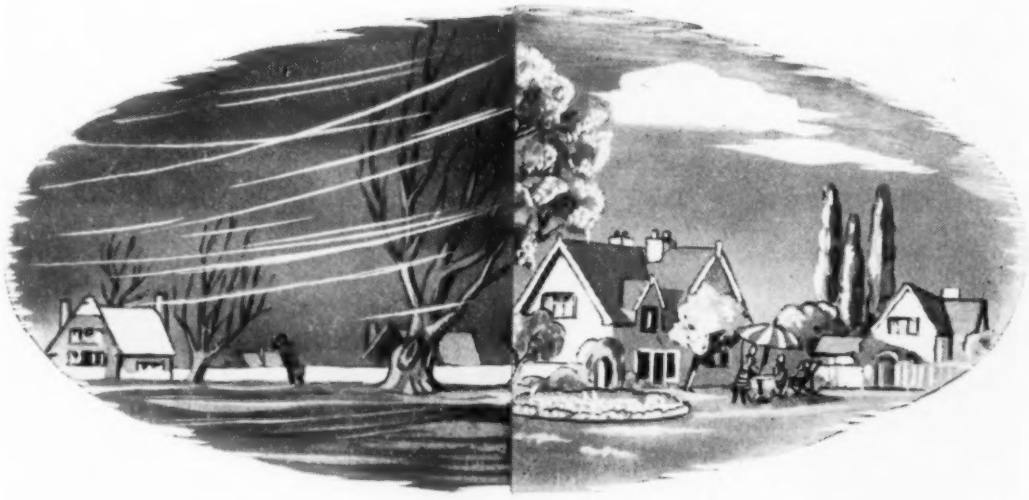

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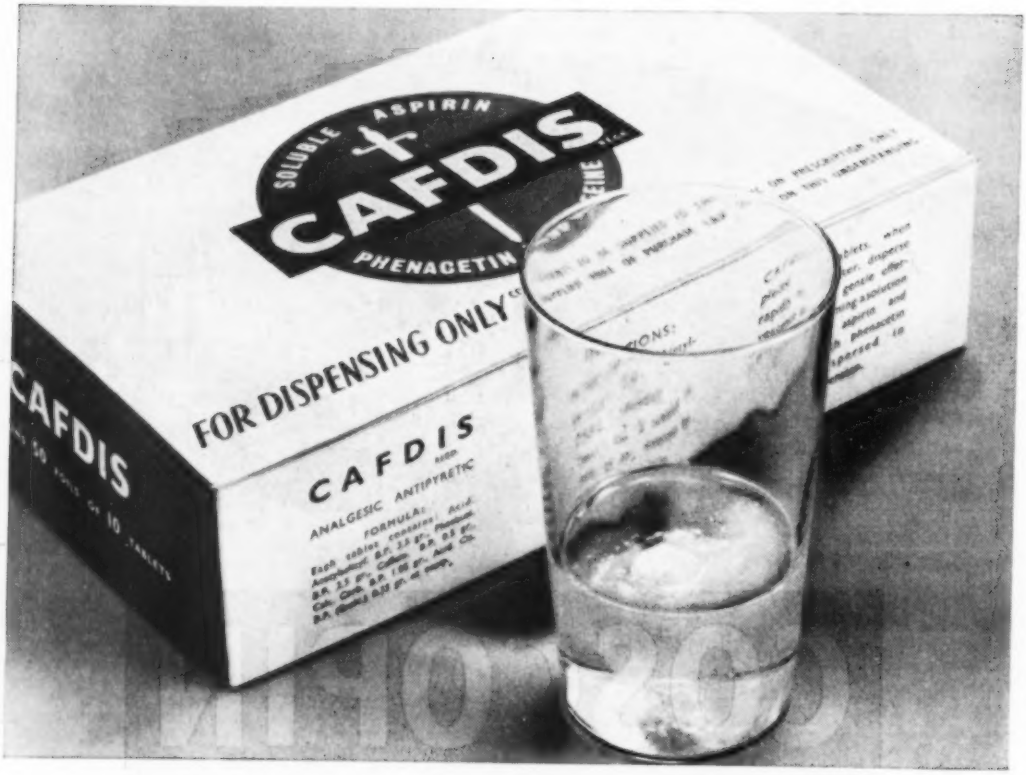

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Obituary

W. E. BARNES, C.B.E., M.R.C.S., L.R.C.P., D.T.M.&H.

Air Vice-Marshal W. E. Barnes, formerly Deputy Director-General of Medical Services of the Royal Air Force, died at Brighton on July 28, four days after his 61st birthday.

William Edward Barnes was born at Finchley on July 24, 1897, and was educated at University College School, Hampstead. He interrupted his medical training at University College Hospital, London, to enter the Royal Field Artillery for service in the first world war, being awarded the French Croix de Guerre in 1918. Returning to University College Hospital in 1919, he qualified M.R.C.S., L.R.C.P. two years later. Entering the R.A.M.C. as a lieutenant immediately after qualifying, he transferred to the Royal Air Force Medical Service in 1922, with the rank of flying officer. For the next seventeen years he served mostly abroad, in Iraq and India, and when the second world war broke out in 1939 he was in charge of a mobile field hospital attached to the Advanced Air Striking Force, with the rank of wing commander. On returning to England he was placed in command of No. 1 Medical Receiving Establishment, and then, in March, 1941, he was appointed commanding officer of Princess Mary's Hospital, Halton. In 1944 he was principal medical officer to the 3rd Tactical Air Force in Burma, becoming deputy principal medical officer at the headquarters of Transport Command, South-east Asia, a year later. On his return to England in 1946 he became principal medical officer at the headquarters of Transport Command, until his appointment as commandant of the R.A.F. Central Medical Establishment. In 1947 he was appointed Deputy Director-General of R.A.F. Medical Services. Three years later he took the D.T.M.&H. of the English Royal Colleges. From September, 1950, he served as principal medical officer, with the rank of air vice-marshal, at the headquarters of Home Command, which at that time took over administrative control of R.A.F. hospitals and medical units in the United Kingdom from Technical Training Command. He retired from the R.A.F. at his own request in 1953. Barnes was a member of the Central Medical War Committee in 1949–50, and in 1954 he was elected to the Council of the British Medical Association, becoming an *ex officio* member of the Armed Forces Committee, of which he became chairman last year. He was appointed C.B.E. and an Honorary Surgeon to the King in 1951, becoming an Honorary Surgeon to the Queen the following year. He married Miss Kathleen M. King in 1923 and had one son.

J. M. K. writes: The name of William Edward Barnes will always have a foremost place among those who built up the medical branch of the Royal Air Force. The record of his service shows this, and points to his devotion and high achievement. But it cannot bring out the qualities which bound him to his friends. He made friends wherever he went and lost none.

He was indeed the best friend anyone could have, considerate to all, courteous almost in the fashion of an earlier day, generous in thought and action, frank when frankness was necessary, completely unselfish; above all—and this was characterstic—he did not change. This stability was perhaps a part of his enviable attitude to life. He saw his duty clearly and did it. He was not in doubt between right and wrong, and never compromised, his principle sustained by his firmness of purpose and his self-reliance. He could be stirred to anger, and three things roused him—slipshod work, evasion of responsibility, and injustice. Faced with these he spoke his mind vividly and to the point. Folding of the hands held no appeal for him, and to his latest days he was active, vital, and interested.

In the earlier years of his service, as a most able clinician, Barnes was meticulous in the care of his patients, seeing to every detail which might be helpful whatever the cost in effort, and not only detail of medical treatment but matters of welfare or of personal or family concern. Any who would come between him and what he thought best for his patients had to reckon with a strong opponent. Later in his service he brought the same clear outlook to the wide administrative problems which fell to his care. His interest in his chosen Service never failed, and after his retirement he was eager as always for its advancement, and jealous for its reputation.

He was a cheerful and stimulating companion, and in his circle liveliness was assured. Those who knew him in the surroundings of his home are grateful for the memory of the real accord and the deep happiness of a united and devoted family. This true man will not be forgotten.

E. W. BAIN, M.B., F.R.C.S.

Mr. E. W. Bain, honorary consulting surgeon to the ear, nose, and throat department of the General Infirmary at Leeds, died at his home at Arkendale, near Knaresborough, Yorkshire, on July 15. He was 81 years of age.

Edward Walter Bain was born on March 11, 1877. He received his medical training at the London Hospital, graduating M.B., B.S. from London University in 1902. Five years later he was admitted F.R.C.S. After graduation he held a number of house appointments at his teaching hospital, and then undertook postgraduate study in Vienna. On his return to London he became senior clinical assistant in the ear and throat department at the London Hospital, assistant surgeon to the Metropolitan Ear, Nose, and Throat Hospital, and surgeon to the ear and throat department of the Royal Waterloo Hospital for Children and Women. A career as a London specialist seemed in prospect for him, but he moved to Leeds in 1912, when he began what was to be a long connexion with the General Infirmary there. For well over thirty years he was surgeon (ultimately senior surgeon) to the ear, nose, and throat department; and the Ilkley Coronation Hospital, the St. James' Hospital, Leeds, and the Castleford, Normanton and District Hospital also had the benefit of his services over a long period. In addition, he was for some time clinical lecturer in diseases of the ear, nose, and throat in Leeds University. During the first world war he served as a captain in the R.A.M.C. at the 2nd Northern General Hospital. When he retired in 1937 he was appointed consulting surgeon in his specialty to the hospitals he had served so well. His retirement, however, was short-lived, for, soon after the outbreak of the second world war in 1939, he was recalled to active work, finally retiring in 1947.

O. C. L. writes: Edward Walter Bain came to Leeds from the London Hospital in 1912 on his appointment as surgeon to the ear, nose, and throat department of the General Infirmary at Leeds. It was to be a happy association lasting in an active way for almost thirty-five years, for he retired in 1937 but returned at the outbreak of war and remained in practice until 1947. He had a large, successful practice which extended throughout Yorkshire and the north, and his services were in big demand when the surgery of the acute mastoid was an important part of otology. He was a careful and deliberate surgeon with a leaning towards conservatism. He had a most equable and calm temperament and nothing ever seemed to disturb or excite him. He was extremely kind and courteous to all patients.

The generous hospitality of "Bill" Bain and his wife will be remembered by many older colleagues and friends who had the opportunity and pleasure of being entertained in the delightful houses they occupied; houses which were graced by beautiful old furniture, of which Bill Bain was no mean connoisseur. For many years he played golf at Alwoodley, and many of us, as students, first met Bill Bain when he organized the annual staff v. students match—and what a delightful encounter it was. In later years he became an enthusiastic fisherman, but throughout his life

his garden gave him greatest joy, and he was tending his flowers only a few hours before he died. During the last few years a neuralgia caused him a good deal of distress, but he was always happy to welcome old colleagues and friends to his home in Arkendale, and with great delight would show them round the garden and entertain them to tea. The death of his wife in 1943 was a severe blow to him, but he was fortunate to be cared for to the end by those who had served him loyally for almost forty years.

P. P. DEBONO, O.B.E., M.D., F.R.C.S., D.P.H.

Professor P. P. Debono died on June 3 in Malta, where for many years he was senior surgeon at the Central Hospital and professor of surgery in the university. He was 67 years of age.

Peter Paul Debono was born on June 29, 1890, and graduated M.D. from the University of Malta in 1910. As first student in his course he won a scholarship which took him to London for postgraduate study, and in 1911 he obtained the Cambridge D.P.H. Returning to Malta, he was assistant to the professor of anatomy and of pathology in the university until 1917. During the first world war he was acting pathologist at the Central Hospital, Malta, and civil surgeon attached to the Royal Navy and, later to the R.A.M.C.; assistant to the pathologist, Malta Command; and officer in charge of a district laboratory. After a period as medical officer of health in Malta in 1918–19, he returned to England for postgraduate surgical studies at St. Bartholomew's Hospital, and was admitted F.R.C.S. in 1920. In the following year he held the appointment of resident surgical officer at Manchester Royal Infirmary. From 1921 to 1926 he was junior surgeon at the Central Hospital, Malta, and he then became senior surgeon and professor of surgery in the university, retiring in 1951. From 1936 to 1939 he served on the Executive Council of Malta, and shortly after the beginning of the second world war he became chief surgeon of the emergency medical services. He was appointed O.B.E. in 1944. Elected to the Maltese Legislative Assembly in 1947, he became Minister of Health and, subsequently, Speaker of the Assembly. He was a member of the British Medical Association for forty-five years, being assistant secretary of the Malta Branch from 1919 to 1923, honorary secretary and treasurer from 1923 to 1930, and president from 1935 to 1937, and again in 1942–3. He leaves a widow and two daughters.

V. G. GRIFFITHS writes: Professor P. P. Debono established modern surgery in Malta. He combined in the highest degree intellectual abilities and skilled craftsmanship, and, coming to surgery by way of physiology and pathology, he proved an ideal teacher whose precept and example founded a sound surgical school in the island. His versatility was remarkable, and he had more than made his mark in bacteriology and pathology before his superabundant energies were providentially turned towards surgery. Even in his most hectic surgical period, however, his interest in natural history never flagged, and his students habitually regarded him as their mentor in practically every subject of the medical curriculum.

During the first world war, when Malta was "the Nurse of the Mediterranean," he was inspired by contact with Sir Charles Ballance and men of similar calibre who were treating the wounded from Gallipoli. His training in England made of him a teacher of the British school, and he was very well known to the leaders of British surgery of his time. The second world war, in which Malta occupied a most honourable front-line position, brought him the burden and the glory of treating almost single-handed the thousands of serious civilian casualties of enemy bombing: it is safe to say that no surgeon in the Commonwealth had a task of equal magnitude in operating for months and months of continuous bombardment in makeshift hospitals with the slenderest resources. Yet throughout that period he also coped successfully with routine surgery and with his teaching.

P. P. Debono was a true general surgeon of such high quality that the results of his incursion into any part of the human body could bear comparison with those of most specialist surgeons. His approach to surgery was lion-hearted, and his courage was matched by superb judgment and marvellous dexterity. He reached the peak of his achievement when he was yet denied those ancillary advances of anaesthesia and chemotherapy that we now almost take for granted. Surgery was not made easy for him, but he did seem to make it easy for others. He was magnificent in times of stress, when his own broad shoulders seemed made for the burdens of all around him: very seldom was he known to lose patience with his assistants, and never to stoop to blaming them when things went awry. He has created in Malta an example and a tradition which his pupils and successors are honoured in attempting to preserve.

CORRIE HUDSON, C.B., C.I.E., D.S.O., F.R.C.S.Ed.

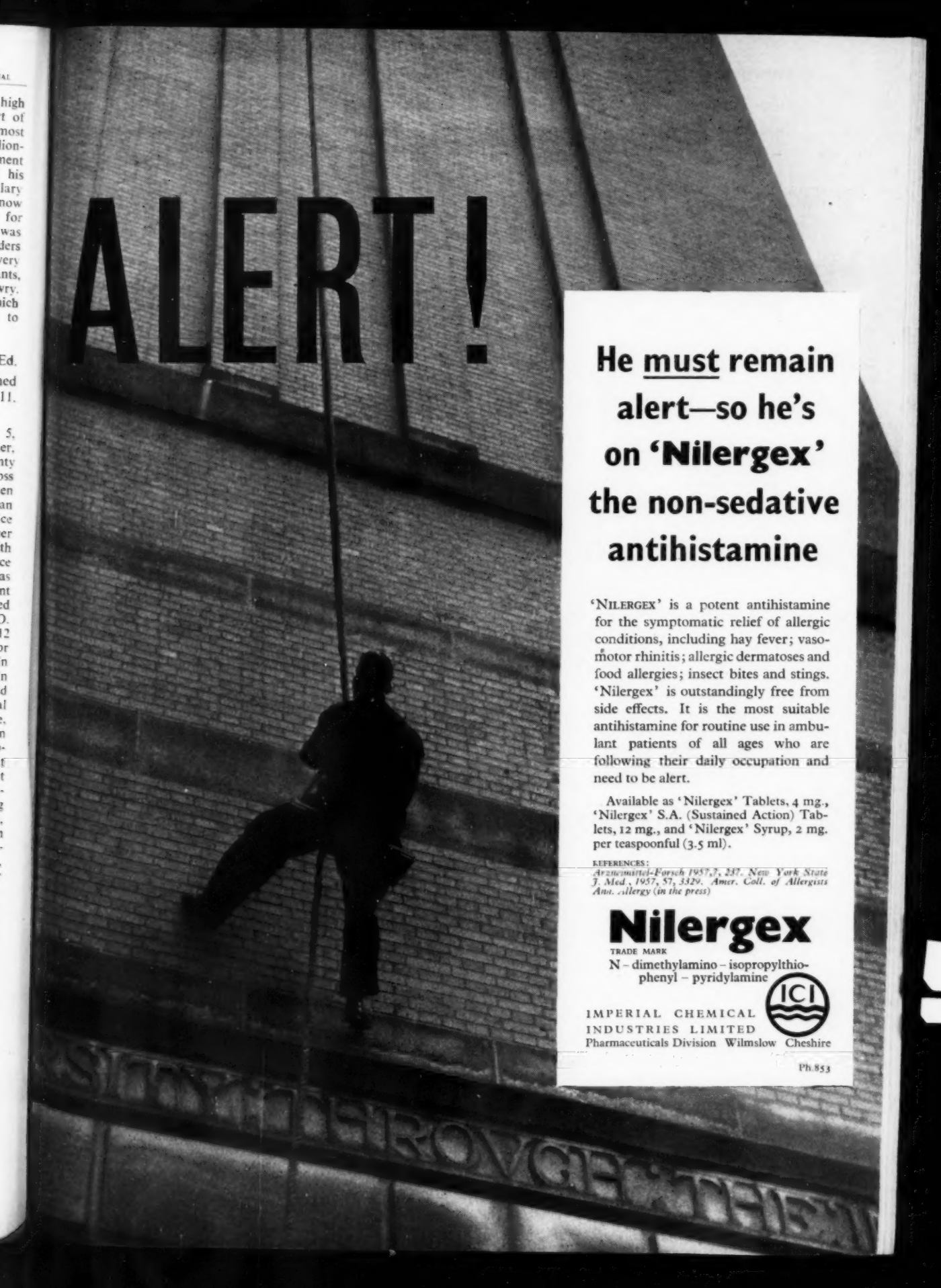
Major-General Corrie Hudson, who had a distinguished career in the Indian Medical Service, died on July 11. He was 84 years of age.

Corrie Hudson was born at Clifton, Bristol, on April 5, 1874. Educated at Manilla Hall, Clifton, where his father, C. T. Hudson, F.R.S., was headmaster for some twenty years, he received his medical training at Charing Cross Hospital, qualifying M.R.C.S., L.R.C.P. in 1897. He then held the appointments of house-surgeon and house-physician at Charing Cross before entering the Indian Medical Service in 1899. From that year until 1907 he was medical officer with the 2nd Queen's Own Rajput Light Infantry, and with that regiment served with the China Expeditionary Force in 1900–2, becoming captain in the latter year. He was with the Somaliland Field Force in 1903–4 and was present at the action at Jidballi. His services there were recognized by a mention in dispatches and the award of the D.S.O. in 1904, as well as the medal and clasp. From 1908 to 1912 he was staff surgeon at Bangalore, promotion to major coming in 1910, and in 1912–13 he served in the war in the Balkans. He was elected F.R.C.S.Ed. in 1912. In November, 1914, soon after the outbreak of the first world war, he was appointed deputy assistant director of medical services with the 1st Indian Cavalry Division in France, and held the post until June, 1916, being mentioned in dispatches for his services. From 1918, when he was promoted lieutenant-colonel, to 1919 he was an instructor at staff schools in India, and from 1919 to 1923 an assistant director of medical services—first, with the Lines of Communication of the Waziristan Field Force in 1919–20, being mentioned in dispatches, awarded the medal, with clasp, and appointed C.I.E. in 1920; then with the Wana Column in 1921–1, again being mentioned in dispatches and receiving the clasp; and with the Razmak Field Force in 1922–3, with a further mention and clasp. In 1924–5 he was director of medical organization for war at Army Headquarters. He became colonel in 1925, and in 1927 was appointed C.B. From 1928 to 1932, when he retired, he was deputy director of medical services in the Eastern Command, with the rank of major-general, and an Honorary Surgeon to the King. His elder brother, Lieutenant-Colonel Charles Tilson Hudson, who died in 1948, also had a distinguished career in the Indian Medical Service. In 1904 Corrie Hudson married Miss Frances E. Barratt, by whom he had one daughter. Mrs. Hudson died in 1945.

KEITH CHITTY, M.B., F.R.C.S.

Mr. Keith Chitty, consultant surgeon to the mid-Worcestershire group of hospitals, died at his home at Chaddesley Corbett, near Kidderminster, on July 9. He was 38 years of age.

Keith Chitty was born on May 12, 1920, the son of Mr. Hubert Chitty, F.R.C.S., of Bristol. From Clifton he won an exhibition to Peterhouse, Cambridge, in 1938, and from



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there he went on to University College Hospital to receive his clinical training, distinguishing himself by winning the Erichson prize in practical surgery. He qualified by taking the London Conjoint Diploma in 1943, and in the following year he graduated M.B., B.Chir. After holding the appointment of house-surgeon at University College Hospital, he served in the R.A.M.C. from 1944 to 1947. On return to civilian life he was appointed surgical registrar at his own teaching hospital, and in 1949 he obtained the F.R.C.S. From 1952 to 1957 he was a senior registrar at Bristol Royal Infirmary, for the first three years in the urological department, and then in general surgery. Last December he was appointed consultant surgeon to the mid-Worcestershire group of hospitals. He leaves a widow.

A. M. writes: The sudden death of Keith Chitty at the age of 38 when he seemed to be at the beginning of a satisfying surgical life has saddened his many friends. He had been appointed consultant surgeon to the mid-Worcestershire group of hospitals as lately as December 1, 1957, and had barely had time to begin his work there. Although he went almost straight away into the Army after qualification, and was among other things medical officer to the Royal Engineers who built "Mulberry Port," his interests were always in surgery and led him to be a surgical trainee when serving later in India until he left the R.A.M.C. in 1947. An interest in genito-urinary surgery and the prospect of returning to the West Country brought him as senior registrar to the urological department in Bristol in 1952. Here the greater responsibility and the wider practical experience produced an immediate response, and Keith Chitty developed into a clinician whose soundness and judgment were respected by all; he was an excellent example of the happy result of combining a sound basic knowledge of surgery with a kindly, reassuring manner and a real ability to inspire confidence in his patients. After three successful years in urology he changed over to general surgery and spent his last two years, before obtaining a consultant post, as senior registrar at the Bristol Royal Infirmary. His friends in the Bristol hospitals were legion: he was greatly liked by his colleagues, and his relationship with his chiefs was on the terms of a personal friendship. He was beloved by the nursing staffs and especially by the students, whom he taught thoroughly and with humour the basic bedside clinical surgery of which he was a master. It is true to say that he left Bristol with universal good wishes, and the news of his death was received with dismay and with the feeling that the world of surgery has been suddenly and unaccountably deprived of a member whose value and potential influence for good were very great indeed. His mother and father and his wife have our sincere sympathy in their tragic bereavement.

Dr. A. G. FREEMAN writes: The news of the death of Keith Chitty at the early age of 38 has been received with great sorrow by his many friends in Bristol. His loss has been keenly felt, especially by the junior hospital staff. As chairman for some time of the south-western regional junior hospital staff group and member of the executive committee of the group council he had done much to encourage and promote the welfare of his junior colleagues. Although he died on the threshold of his career as a consultant surgeon, the many appreciations received from his surgical colleagues of his work and skill speak for themselves. However, it is not in a professional capacity that I wish to add my personal tribute but rather as one who has had the immense privilege of friendship since we were undergraduates together at Cambridge some twenty years ago. Even in those days Keith knew that, like his father, he would become a surgeon. Soon after qualification his training was interrupted by war service, and as an Army doctor he landed in Normandy on "D" day. On demobilization he resumed his surgical training, and a few months before his death had achieved his ambition. To the casual acquaintance Keith may have appeared somewhat quiet and retiring in manner. Yet to those who knew him well it soon became evident that here was a man with a fine sense of humour and with high ideals and a firmness of character which were to be admired. His quiet and friendly nature bred trust and respect. Before he left Bristol at the end of last year the housemen and registrars in the area gave a dinner in honour of Keith and two of his colleagues who had recently obtained consultant appointments. We felt at that time that we were wishing godspeed to our friends. Now we in Bristol mourn the loss of one who will be sadly missed, and our sincere sympathy goes out to his wife and to his family in their bereavement.

W. H. C. SPOONER, M.B., B.S.

Dr. W. H. C. Spooner's untimely death on August 1 through the ramming of his yacht by a tug at Brest has caused consternation and sorrow in the town and district of Blandford Forum, Dorset. He was 49 years of age.

William Henry Casswell Spooner was born on July 2, 1909, at Blandford, where his father, grandfather, and great-grandfather were all in general practice before him. Educated at Epsom College and at St. Mary's Hospital, he took the London Conjoint diploma in 1932 and the London degrees of M.B., B.S. two years later. After a period of residence in hospital and acting as assistant in Llandudno, he returned to his birthplace in 1936, where he went into partnership with Dr. K. J. T. Wilson and Dr. D. Oliver, following the retirement of Dr. L. Bodley Scott, and since 1954 also with Dr. D. I. T. Wilson. His knowledge of the locality, his sympathy, kindness, tact, and skill, enabled him to build up a large practice in a short time, and he held the esteem and affection of all who knew him. During the second world war he left his practice to serve as a medical officer in the Royal Air Force, attaining the rank of squadron leader. Apart from his work, his chief interests lay in yachting and in art. He was instrumental in founding the Blandford Forum Club and in organizing local art exhibitions. A physician, counsellor, and friend to his patients, a grand colleague, who always gave of his best, he continuously radiated to his friends, colleagues, and patients the finest qualities of his profession. He was a faithful and devoted servant to the people of Blandford and district, and both they and his partners have suffered an irreparable loss. The greatest burden of grief and sense of loss falls on his widow and three children, and to them the town and countryside and his fellow practitioners extend the most sincere sympathy.—K. J. T. W.

A. K. COSGRAVE, *M.C.*, M.B., B.Ch., L.M. D.P.H., D.T.M.&H.

Dr. A. K. Cosgrave, who was for many years a member of the Colonial Medical Service, died suddenly at Beaconsfield on June 20.

Alexander Kirkpatrick Cosgrave was born in 1885, and was a medical student at Trinity College, Dublin, graduating M.B., B.Ch. in 1909. Soon after graduation he went out to the Straits Settlements as a surgeon in the medical department there. When the first world war broke out in 1914 he was on leave in England and immediately joined the R.A.M.C., serving until the end of the war and attaining the rank of major. In 1918 he was awarded the Military Cross for his services. In the same year he obtained the Dublin D.P.H., and in 1920 the L.M. at the Rotunda Hospital and the D.T.M.&H. of the English Royal Colleges. In 1921 he transferred to the health branch of the medical department in the Federated Malay States to become health officer to the state of Negri Sembilan, where he did very good work, especially in connexion with the sanitation of the very malarious town of Gemas. Later, he was transferred to Kuala Lumpur as health officer, subsequently becoming senior health officer. In 1929 came a change in the medical organization. The federal post of chief health officer was abolished and the posts of senior health officer and senior medical officer, which existed in each of the four states of

the federation, were amalgamated to form for each state one combined medical and health administration. Dr. Cosgrave received one of these appointments, which he held until he retired in 1934. A few years before this he was chairman of the Federated Malay States Division of the B.M.A. After his return to Britain he settled at Beaconsfield, but throughout the second world war he again served in the R.A.M.C. A Fellow of the Royal Society of Tropical Medicine and Hygiene, he seldom missed a meeting after his retirement. Throughout his life he got on well with all classes of people, and his many friends will wish to extend their sympathy to his wife and family.

D. R. MURLEY, M.R.C.S., L.R.C.P.
D.Obst.R.C.O.G.

Dr. D. R. Murley, who was in general practice at Mullion, Cornwall, for most of his all-too-short professional life, died on July 6. He was 35 years of age.

David Ronald Murley was born on September 27, 1922, and brought up in Cornwall, where his father, the Rev. D. R. Murley, was vicar of Ludgvan. He was educated at Wellington School, Somerset, and at St. Mary's Hospital, where, after qualifying M.R.C.S., L.R.C.P. in 1945, he was obstetric officer. Joining the R.A.M.C., he served abroad in Saudi Arabia, attaining the rank of major. On returning to this country he was orthopaedic house-surgeon at the St. Mary's orthopaedic unit, at Park Prewett Hospital, and then returned to his beloved Cornwall, where he was in practice at Mullion. In 1949 he obtained the Diploma in Obstetrics of the Royal College of Obstetricians and Gynaecologists.

P. R. G. G. writes: It was with great regret that I learned of the death of Dr. D. R. Murley. As a medical student I shared a flat with him in London until he qualified, and knew him extremely well. Despite his rather serious looks he had a keen sense of humour, and he brought an unswerving loyalty and vigour to every task he undertook. Dr. Murley was also a keen horseman and tennis player, and he had that great gift of getting on equally well with young and old, rich and poor, wherever he happened to be. His death will be a great loss to those who knew him, and sincere sympathy is extended to his widow and two daughters.

C. H. writes: The sudden loss of David Murley is a personal tragedy to all who knew him well. An excellent doctor and a delightful companion, he combined integrity and deep sincerity with a cheerful outlook and ebullient sense of humour. Men of his character and temperament are rare: we shall not replace him in our life.

T. BEN THOMAS, M.R.C.S., L.R.C.P.

Dr. T. Ben Thomas, medical superintendent of Mount Pleasant Hospital, Swansea, and anaesthetist to the Glantawe Hospital Management Committee, died on July 12 after an operation. He was 60 years of age.

Thomas Ben Thomas was born at Swansea on October 23, 1897, and was educated at the Swansea Grammar School, Taunton School, and St. Bartholomew's Hospital. He interrupted his training to serve in the Army in the first world war. After qualifying in 1923 and doing some postgraduate hospital work, he settled in practice in Swansea, where he soon became a well-known and well-liked medical figure in the district. He built up a successful practice, but, much to his patients' regret, gave this up after some years to become medical superintendent of the Tawe Lodge Infirmary. During his lifetime he saw one of his greatest ambitions realized—the gradual transition of a good and well-run Poor Law institution, Tawe Lodge, to a modern and well-equipped and well-staffed hospital, the Mount Pleasant Hospital. He was the ideal person to be in charge during this transition period; it was in no small measure due to his drive, enthusiasm, tact, and perseverance that this change took place so smoothly and so steadily. His home and his hospital were always sources of great joy and great pride to him. Although a busy man, he found time to be one of the honorary secretaries of the Swansea Division of the B.M.A. from 1937 to 1943, and eventually he became a very successful and popular chairman in 1951–2. Later, he acted, also very successfully, as joint charity steward of the Swansea Division, a post he held until his death. He was an active member of his Church and was also a freemason. He became president of the Rahere Society and captain of the Pennard Golf Club.

T. O. L. writes: Ben, as Dr. Thomas was known to us (Dr. Ben to his patients), was a lovable character. His cheerfulness, youthful exuberance, and sense of fun infected both his patients and his colleagues. He lived his life to the full, in work and play. Outstanding among his qualities were his kindness and his desire to help the sick and distressed without thought of himself. We in this community know how difficult it will be to fill the gap left by his death. He will be greatly missed and mourned for many a day by all who knew him, and we, in turn, extend our deepest sympathy to his widow and two daughters. It is a great privilege to have known him.

MARY T. PENRICE, M.B., Ch.B.

Dr. Mary Penrice, who was in general practice at Bebington, Cheshire, for nearly 30 years, died at Clatterbridge General Hospital on July 13 after a short and painful illness. She was 55 years of age.

The only daughter of a Birkenhead sea-captain, Mary Thompson Penrice was educated at Birkenhead and studied medicine at Liverpool University, where she graduated M.B., Ch.B. in 1926. After resident appointments and a short period in practice at Birkenhead, she settled at Bebington in 1930 and worked there whole-heartedly until her last illness. She was well known in the district, not only as a very careful doctor but also as a woman whose advice and help were always freely given to those who sought them. She upheld the highest professional standards, and her death is a blow to her patients and colleagues alike.—G. B.

Medico-Legal

FEMININE BEHAVIOUR

[FROM OUR LEGAL CORRESPONDENT]

Earlier this year (*Journal*, May 17, p. 1187) we reported a case in which the judge held that the behaviour of a husband in dressing up as a woman with the knowledge that it must cause his wife distress, a course of conduct which would ultimately have a serious effect on her health, amounted to cruelty. The wife was granted a decree of divorce. On May 22 Mr. Justice Davies (*The Times*, May 23) had to deal with the petition of another wife. She was married in April, 1950. In May, 1951, a child was born of the marriage, but apparently the husband had started shortly after the marriage to develop female characteristics, at any rate mentally. After consulting psychiatrists in 1952 and 1954 he was sent to hospital for treatment, and was given hormones with the express intention on the part of the doctors to accelerate and facilitate the development in him of female characteristics. The endocrinologist who with psychiatrists had advised this treatment said it was plain that the husband was suffering from a mental illness which made him to some extent feel like a woman and want to be a woman.

In 1957 the husband left his wife because of his desire to become a woman and because he could not stand living with her, and now dressed as a woman and was employed as a woman clerk. This naturally caused his wife revulsion.

Mr. Justice Davies held that the husband's consent to undergo hormone treatment for this mental illness was not cruelty on his part, since he could not help his illness any more than any other illness. He added that if the wife waited until May, 1960, she might get a divorce on the ground of desertion.

Medical Notes in Parliament

COMMONS REVIEW PROGRESS AND PROSPECTS OF HEALTH SERVICE

It was not to be expected that the Commons would allow the tenth anniversary of the National Health Service to pass without making it the occasion for a debate (the House of Lords having already had theirs); nor that on such an occasion Mr. ANEURIN BEVAN, its progenitor as Minister of Health in the 1945–50 Labour Government, would resist the opportunity to emerge from his preoccupations as "Shadow Foreign Secretary" in the Labour hierarchy for a foray into domestic affairs.

The speech with which he opened the debate on July 30 was a racy mixture of pride and politics. He went a long way back, to the period of preparation before the National Health Service Bill was brought, to pay a handsome tribute to the officials at the Ministry of Health, mentioning in particular Sir William Douglas, then the Permanent Secretary, and Sir Wilson Jameson, Chief Medical Officer, but embracing all in an expression of gratitude and appreciation for loyal, efficient, and inexhaustible service. The claim that the facilities the Health Service had provided to the population as a whole could be regarded as a marked success, and that there was general satisfaction with its therapeutic side, Mr. Bevan coupled with some party thrusts. So successful had it been that there was now competition in claiming paternity. He had even found Conservative members who had forgotten that they had voted against it on every occasion and for every conceivable reason. It had been said that all parties were in favour of it, but when he went to the Ministry of Health he found no evidence of that. Opposition was being whipped up—but he had been singularly fortunate in his opponents.

Free for All

Two conceptions underlay the Health Service. The first was to provide a comprehensive free health service for all at time of need. The second, which had been somewhat overlooked, was the redistribution of national income by a special method of financing the Service. On the first principle, there had always been more medical care in existence than the masses had been able to reach. It was that that the National Health Service was intended to put right. To-day, 98% of the population were registered with general practitioners. Not all the credit for the improvement in the nation's health went to the Service; there had been better standards of nutrition, and of housing, and new drugs. But the main point remained: all these drugs and medical facilities would not have been available under the old system. The new knowledge would be there, but it would not reach the people needing it. That was why the medical profession got it all wrong when it started to oppose the Service in 1946. Medical men seemed to believe, or some of them at least pretended to believe, that all nationalized medicine would do would be to interfere in the practice of medicine. He had had no such intention What the Health Service was intended to do was to organize the practice of medicine in such a fashion as to reach the people who needed it most. That had been done.

Tax on the Better Off

On the financial side, he was getting a little worried. The insurance principle had been rejected at the inception of the Service as wholly inapplicable, and it was decided that the best and fairest way to finance the scheme was through the Exchequer, by general taxation, and those who had most would pay most. Conservative Members had been engaged in trying to reverse the redistributive aspect of the Service, and one of their chief supporters was the man who tried to stop it coming into existence at all, Dr. Charles Hill, Chancellor of the Duchy of Lancaster. The Treasury, through Mr. Dalton, took as an appropriation-in-aid that part of the contribution of the old National Health Insurance which had been used for medical benefits, amounting to about £41 millions. It had nothing to do with the Health Service, and was not paid to the Health Service. There was no organic, financial, or administrative link between the two. Although expenditure on the Health Service went up by £200 millions, the appropriation-in-aid remained the same.

The link between insurance and national health had been created in the minds of the Government to justify a tax on the poor. The contribution had been raised to £57 millions in 1957–8 and to £95 millions this year. By assuming the link the Government had called for more money from the National Insurance Fund instead of increasing taxation to provide the additional money. It was a transfer of the burden from the rich to the poor. He resented it because it was inimical to the second principle of the scheme, and because if persisted in it would appear to justify a gradual transfer of the whole cost of the Health Service to the shoulders of the poorest members of the community.

Pay-beds

After a reference to the great mischief done to the Health Service by continual changes in the Ministers at its head, Mr. Bevan turned to the pay-bed provision—a concession which was, in some cases, seriously abused. He received letters about it every week. The consultants, if they could get a paying patient into hospital, jumped the waiting-list and got him in. There was no justification for saying that in every instance it was for medical reasons. It was for financial reasons. He did not for a moment say this was universal, that it was so grave as to impair the Service, but it had caused great grief. He hoped this kind of thing would stop. If it was, the whole climate of the Service would be much happier, and the hospitals much more wholesome. If it was not stopped, then, in spite of the fact that some consultants might take him to court, he would send their names to the Minister—and not even try to claim qualified privilege.

Minister's Reply

Mr. D. WALKER-SMITH, Minister of Health, began his reply with some ripostes to Mr. Bevan's "highly selective remembrances" of things past, acknowledging in the process that no one would wish to grudge him any of the credit due for the inception of the Health Service, but was more concerned with the pattern of the future. One of the things that had turned out better than some had expected in the 10 years had been that the strength of the voluntary work in the Health Service and hospital work had continued unabated. There was still a sound basis of voluntary work, freely given and highly regarded.

The country was getting a good bargain for the very large amount the Health Service was costing. There was an increase in the number of effective beds in hospitals, greater speed and efficiency of treatment, and a great increase in the range of drugs to heal and vaccines to prevent disease. But there was not a universal pattern of success to match the conquest of diphtheria and the approaching conquest of tuberculosis. On the other side was the upward curve in cancer of the lung, leukaemia, and arteriosclerotic diseases. In this, as so often in this imperfect world, the successes left their problems. By increasing the expectation of life they put greater emphasis on the malignant and degenerative diseases of the later years.

Value of Prevention

Two signposts to future action were provided by the success with tuberculosis and diphtheria. One was the importance and potential of preventive medicine and action; and second, the contribution that could be made towards a solution of the accommodation problem in hospitals by the virtual elimination of some diseases. He was anxious to apply the principle of preventive medicine wherever possible. A heavy programme of vaccination

against poliomyelitis had been carried through this summer. One had to tread very delicately on this unpredictable ground, but it was perhaps significant that up to and including the 29th week of this year there were fewer cases, and fewer paralytic cases, than in the same period in any previous year, and the figures were far below the average. Another promising preventive measure was the fluoridation of water supplies against the incidence of dental decay. He hoped that in the areas concerned the people would appreciate its benefits and understand that there was no harmful effect from it. Mr. J. BAIRD (Wolverhampton, North-East, Lab.) here interrupted that the results of the experimental schemes could not be studied until 1962. Why not take action now, on the ample evidence from towns in England and from the U.S.? Mr. WALKER-SMITH told him they would rather see a continuance of the policy of demonstration on which they were embarked.

Planning for an Ageing Population

The impact of age structure on the changing pattern of disease was one of two great special problems which must condition thinking and planning for the future of the Health Service. By 1975 one person in seven would be over 65 years old, compared with one in 21 at the beginning of the century. Extended expectation of life must be accepted as a challenge to be met. There was a double duty: socially, to see that the increased span of life was a time of happiness; and economically, to see that looking after the old did not place an undue burden on the working community. The policy, therefore, was to seek to keep the elderly in their homes as long as possible, and when they had to go to hospital to rehabilitate them wherever possible. Two encouraging developments were that there had been a steady rise in attendances at chronic sick and geriatric clinics (from 7,000 in 1950 to 39,000 last year); and on the in-patient side, although there had been only a small increase in the number of beds a better use of them had enabled more patients to be treated. There were now over 70 geriatric departments, and more would be set up as resources permitted.

The other great special problem was mental health. More than two out of five hospital beds were devoted to those suffering from mental disorder. The Royal Commission had recommended, among other things, the abandonment of the assumption of the need for compulsion in favour of the offer of care without deprivation of liberty. The review of existing patients he had asked for in January to give effect to this as far as possible without legislation was in progress. Approximately 18,000 recommendations for discharge from compulsory powers had been received by the Board of Control, and about 12,000 accepted. Only about 100 had been refused. Examination of the remainder was continuing. Over the whole field of practice and procedure in mental health, Parliament would have the opportunity when the time came for mental health legislation to add to the volume of social progress a notable new chapter on this very human theme.

Efficiency in Hospitals

Whatever success was achieved in the policy of out-patient treatment, there would always be an important residue calling for in-patient treatment. The hospital service would always loom large; running costs took 54% of expenditure on the Health Service. Obviously it was necessary to seek the highest common factor of efficiency and economy. Organization and method studies were a constructive challenge to tradition, and should be accepted as such. The results could be dramatic, particularly in manual work. These potential savings were a hidden reserve of the greatest value. The development of this work should be encouraged, and its good results demonstrated to hospital authorities as fully as possible. The present experimental unit in the Ministry was to be enlarged and made permanent. A group of management consultants had offered to undertake a series of surveys at their own expense to demonstrate the economies and improvements in efficiency which could be achieved in the hospital service. He had accepted the offer, and had suggested four subjects for investigation. The Royal College of Nursing had suggested that an advisory council on work study should be set up, and he would consult the other interests involved before settling the role and membership of the council.

Points from the Debate

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.), speaking about mental illness and overcrowded hospitals, said he hoped the Minister would resist pressure to build new hospitals to relieve the congestion. Mental cases should be sent into residential hospitals only if that was absolutely unavoidable. He advocated the extension of day hospitals, out-patient departments, psychiatric clinics, and domiciliary services.

Mr. JOHN CRONIN (Loughborough, Lab.), on the theme that neither doctor nor consultant had any incentive to consider economic questions, said that general practitioners were competing to obtain patients, and had a more or less blank cheque on the finances of the Service. Similarly consultants, in prescribing and ordering ordinary treatment, were completely autonomous. There was no doubt it would be possible for hospital consultants to treat patients more economically. The medical profession had co-operated with the Health Service in a remarkable way, but few had any idea of the economics of the Service. There was a case for some sort of administrative control of the medical profession itself.

Dr. EDITH SUMMERSKILL (Warrington, Lab.) deplored the general practitioner's lack of adequate training in psychiatry. Prescriptions were often written solely to terminate a protracted but necessary interview in a busy surgery with a patient suffering from some form of neurosis. Did the system that had been evolved encourage a doctor to be frank, and to refrain, whenever possible, from sending people to hospital? The surgical waiting-lists were so long, and falling so slowly, that more facilities were needed. She invited the Minister to consider territorial redistribution for long waiting-lists.

Parliamentary Secretary Winds Up

Mr. RICHARD THOMPSON, the Parliamentary Secretary, in his reply to the debate, expressed general agreement with the points made by Dr. Broughton, and assured him that the kind of objectives he had in mind were desirable ones that the Ministry intended to pursue.

The general practitioner was the key man in the non-hospital medical services. Through the executive councils and in other ways they wanted to build up his position in the Health Service and to ensure that it was one of proper status and importance. It was not true, as had been suggested, that because of insufficient co-operation among the various arms of the Service the general practitioners were working in isolation. The increase in partnerships, which helped to produce effective co-operation, had been notable. There were now about 68% of practitioners in partnership, compared with 50% in 1948. Group practices had also been encouraged with the aid of loans.

Of the drug bill, estimated to cost £74 millions, he pointed out that 40% would go to chemists for overheads and the services they provided, and 60% for the wholesale cost of drugs and dressings. An inquiry in 1955 revealed no evidence of excessive prices, but the Ministry were quite prepared to renew the inquiry if they judged it necessary. The scheme for voluntary regulation of prices covered 90% of proprietary preparations. When first applied in 1957 it resulted in 285 price reductions and an estimated saving of £400,000 a year. A much more substantial final report from the Hinchliffe Committee was on the way, and the closest attention would be paid to the recommendations. Some immediate administrative steps were being taken on the interim recommendations, and the appropriate organizations consulted on further action.

MEDICAL ACT, 1956

The Medical Act, 1956 (Amendment), Bill was read the third time and passed in the House of Lords on July 24, and on August 1 received the Royal Assent.

PNEUMOCONIOSIS AND BYSSINOSIS APPEALS

The Draft Pneumoconiosis and Byssinosis Benefit Amendment Scheme, 1958, was approved by the Commons on July 24. Mr. W. VANE, Parliamentary Secretary, Ministry of Pensions and National Insurance, explained that the Pneumoconiosis and Byssinosis Benefit Act was designed to bridge the gap between the old Workmen's Compensation Acts and the new Industrial Injuries Act. The adjudication provisions followed the pattern of the compensation Acts, and the decision on the cause of death was made by the Silicosis Medical Board, from which there was no appeal. The draft scheme was in no sense a criticism of the board, but experience had shown that this could be improved and some appeal allowed. The decisions were not wholly medical; there were also legal implications. The draft scheme substituted the adjudication procedure familiar under the Industrial Injuries Acts. The cause of death would be determined by the insurance officer, with medical advice, and from his decision a right of appeal would lie to the local appeal tribunal, and there could be a further appeal to the Commissioner. No large number of appeals was expected, but experience suggested that a few people would have been better satisfied if they had been able to exercise a right of appeal.

QUESTIONS IN THE COMMONS

Charing Cross Hospital

Mr. G. RIPPON (Norwich, South, C.) asked the Minister of Health on July 29 whether he had reached a decision regarding the future of Charing Cross Hospital.

Mr. WALKER-SMITH stated that on February 9, 1955, the House was informed by the then Minister that the Government's plans for hospital building expected to start in the next few years included a project for the rebuilding of Charing Cross Hospital at Northwick Park, Harrow. This proposal had had to be abandoned because further consideration by the University of London and the University Grants Committee caused these bodies to decide that it was not in the best interests of medical education to remove the Charing Cross Hospital Medical School to Northwick Park.

The existing Charing Cross Hospital building is outmoded and inadequate for hospital purposes and it cannot be properly redeveloped on the same site. To meet university requirements the new site must be within reasonable access of all the facilities of the university, including the basic sciences and general student activities, and in August last the responsible hospital authorities were asked to consider the possibility of rebuilding on the site of the existing Fulham Hospital, which was in close proximity to these university facilities and which also required rebuilding.

I am glad to say (he continued) that a large measure of agreement has been reached by the responsible hospital authorities about the practicability of amalgamating Charing Cross Hospital, the West London Hospital, the Fulham Hospital, and the Fulham Maternity Hospital as a first step towards the ultimate replacement of all of them by a new general teaching hospital at Fulham.

I have given close and careful consideration to all the representations made to me, including those made by the committee headed by the Mayor of Fulham, and I am satisfied that the Board of Governors of Charing Cross Hospital in close co-operation with the South-West Metropolitan Regional Hospital Board will provide a service to the locality which will compare favourably with that which might have been provided by the rebuilding of Fulham Hospital as a non-teaching hospital. I propose, therefore, to make arrangements for the proposed regrouping at the earliest practicable date so that the replanning of the new teaching hospital may proceed without delay. The necessary facilities for clinical teaching will be provided at the new hospital, but the question of preclinical facilities is under consideration in consultation with the university and the University Grants Committee.

Scope of Inquiry into Artificial Insemination

Mr. R. A. BUTLER, Home Secretary, announced on August 1 that the terms of reference of the proposed committee on human artificial insemination were to be

To inquire into the existing practice of human artificial insemination and its legal consequences and to consider whether, taking account of the interests of individuals involved and of society as a whole, any change in the law is necessary or desirable.

The Earl of Feversham had agreed to serve as chairman. He hoped shortly to announce the names of the other members of the committee.

Russian Multiple Sclerosis Vaccine

Mrs. JOYCE BUTLER (Wood Green, Lab.) asked what further details the Minister had been able to obtain of the New Zealand experience of the Russian multiple sclerosis vaccine. Mr. WALKER-SMITH replied that he had received no further details from New Zealand. The replies received to inquiries which were addressed to the Soviet Union were being studied.

A letter published in the *British Medical Journal* for July 26, from Dr. A. K. Shubladze, of Moscow, and Professor G. W. A. Dick, of the Queen's University, Belfast, said that they thought it clearly necessary to reinvestigate and characterize the original isolates of the virus from which the vaccine was prepared, as recent experiments had shown that the strain in current use was similar to rabies virus. So far as treatment with the vaccine was concerned, they said that it was not possible to make any further recommendation until reinvestigations had been made. This latest information made it clear that both the efficacy and the safety of this vaccine were at present in doubt.

B.M.A Conference and Merit Awards

Mrs. JEGER (Holborn and St. Pancras, South, Lab.) asked the Minister what communication he had received from the British Medical Association's annual conference on the subject of merit awards; and what reply he was making thereto. Mr. WALKER-SMITH: None.

Institute of Criminology

Mr. BUTLER announced on July 31 that he had been informed by the Vice-Chancellor of Cambridge University that, provided the necessary funds could be made available, the university would be glad to consider the establishment of an institute of criminology, whose functions would include both teaching and research, as well as facilities for exchange of views and information with those concerned with the practical administration of the law. The nucleus of the institute would be the existing Department of Criminal Science, but it would be developed on a broader basis, and steps would be taken to associate all interested faculties with its management.

Universities and Colleges

UNIVERSITY OF DURHAM

At Congregations held on July 4 and 5 the following degrees and diplomas were conferred:

M.D.—G. S. Anderson, *G. Pringle, *G. A. Stirling.

M.B., B.S.—J. Anderson, W. V. Anderson, Margaret S. Atkins, Judith C. H. Bullen, Margaret S. Burrill, Mary Bynon, I. G. Campbell, J. Cape, Jean Carr, Ben-Zion Chalk, J. R. Cox, W. G. Donald, C. M. Dunn, L. E. Dunn, Elizabeth Elliott, M. A. Ferri, G. Gill, C. P. Gillie, H. L. Goldwater, R. Heslop, D. H. Irvine, Fiona M. Lehmann, Margaret A. Lewis, T. Lind, J. B. McCafferty, A. J. McComas, C. H. McCulloch, A. Malcolm, P. F. Moran, J. M. Morrison, H. N. Murray, H. Natvig, Sarah H. J. Nelson, S. A. Oduntan, I. L. T. Ohuwole, A. Powney, D. G. Proudler, D. N. Raine, D. Rankin, M. F. Reece, E. Ross, Dorothy A. Stevenson, J. R. C. Stubbs,

Margaret A. Stubbs, E. Taylor, I. H. Taylor, S. Tetlow, Jean B. Thompson, P. R. Uldall, M. Ward, Joan M. Whitmore, P. G. Wood, P. H. Yorke, *P. M. Calamel.

DIPLOMA IN PUBLIC HEALTH.—Jean M. Bainbridge, Florence Cadogan, Marion Harrison, T. W. L. Knaggs, June K. Lloyd, R. T. Pagan, Doris Story.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—E. S. Lower.

*In absentia.

UNIVERSITY OF MANCHESTER

The following candidates have satisfied the examiners at the examinations indicated:

D.P.H.—Margaret Armitstead, H. Bailey, Irene S. Bailey, A. D. Bostock, J. R. Brown, A. S. Dunn, B. R. Ellis, A. Gatherer, R. E. Jones, W. Lees, Joyce E. Leeson, J. E. Morris, D. W. Preston, Rachel D. R. Sasieni, H. R. Simpson, D. H. Vaughan.

UNIVERSITY OF BIRMINGHAM

Professor W. Melville Arnott will represent the University at the second World Conference on Medical Education to be held in Chicago from August 29 to September 4, 1959.

Mr. A. L. d'Abreu has been appointed to the board of governors of the United Birmingham Hospitals.

Professor J. W. Orr has been reappointed to the Birmingham Regional Cancer (Co-ordinating) Committee for the year ending March 31, 1959.

The title of University Research Fellow has been given to the following during the tenure of their present posts: *Department of Medicine*, Dr. L. A. G. Davidson, senior medical registrar, Queen Elizabeth Hospital; Dr. Mary Bateman, Endowment Fund Research Fellow, Queen Elizabeth Hospital; Dr. N. Segel, Nuffield Fellow. *Department of Experimental Pathology*, Dr. G. M. Aber, medical registrar, Queen Elizabeth Hospital.

Dr. F. N. Garratt has been appointed Research Fellow in Social Medicine from July 1, 1958.

The following have resigned their appointments from the dates indicated in parentheses: Dr. K. Aterman, Senior Lecturer in Biophysics in the Department of Anatomy (July 31, 1958); Mr. P. G. Bevan, Lecturer in Surgery (July 15, 1958); and Dr. K. R. Thornton, Lecturer in Pathology (September 30, 1958).

The University has accepted the offer of Dr. Arthur Beauchamp, a former student of the Medical School, to endow an annual prize to be awarded for the best essay on some aspect of general practice.

In Congregation on July 5 the following degrees were conferred:

CH.M.—K. D. Roberts, R. W. Tudor.

PH.D.—*In the Faculty of Medicine:* [5]L. Kornel, J. C. Lawrence, D. G. Moulton.

M.B., CH.B.—[1 2]A. J. G. Campbell, [1 2 4]F. J. Fawcett, [1 6]B. Goodhead, T. R. Abbott, Ada M. Adams, D. Atkinson, Ann I. Ballantine, A. D. Barnes, Ruth Barton, Vivien E. Basco, L. S. Bernstein, [2]C. Berry, J. E. Bewley, K. S. Bhogal, H. E. Black, A. W. Burdon, Brenda M. Chant, A. C. Cottrill, D. C. Crawford, J. T. Davies, P. W. Davis, D. G. Emery, Sylvia D. Gardner, Catherine M. Gay, [3 7]J. R. Geddes, [8]Jean M. Gibbon, S. Glick, M. G. S. Golby, I. G. Goldman, R. W. Griffin, R. G. Harrison, Frances E. Heron, M. J. Hoare, G. B. Hunt, S. E. O. Jones, M. Joomye, [4]Menigha Kemmer, [7]A. B. Lavelle, M. Lewis, Edna J. Lloyd, Wendy I. McNeilly, G. L. Morgan, Philippa N. Mourant, M. G. Mullan-Feroze, [7]K. Newbold, D. M. Nicoll, B. A. Oni-Okpaku, C. E. Ounard, Doris H. Pereira, C. R. Phillips, P. R. Preston, Susan E. M. Richards, [2]C. J. Roberts, R. N. Smith, D. B. Southall, [8]Sheila M. Statham, Margaret S. Taylor, [4 8]C. W. Thompson, [2 8]F. R. Walford, A. West, Nora E. Wild, T. H. Williets, P. J. Witherow, D. A. K. Woodward.

The following scholarships and prizes were awarded: *Queen's Scholarships*.—Final year, F. J. Fawcett; Fifth year, A. Rhodes. *Ingleby Scholarships*, J. R. Geddes (obstetrics and gynaecology), A. J. G. Campbell (paediatrics and child health). *Special Undergraduate Scholarships*, A. R. Beebeejaun, G. B. Gelling, Margaret G. Hudspith, E. A. Jones, H. G. Percival, Diana M. Price, K. Prowse, D. Sampson, M. Thomas, W. J. A. Westwood. *Arthur Foxwell Memorial Prize in Clinical Medicine* and *Beckwith Whitehouse Prize in Obstetrics and Gynaecology*, F. J. Fawcett. *Sampson Gamgee Memorial Prize in Surgery* and *Joseph Sankey Prize in Clinical Surgery*, C. W. Thompson. *"Queen's Hospital" Joseph Sampson Gamgee Prize in Surgery*, A. D. Barnes. *Cyril Raison Prize in Surgical Diseases in Children* and *Russell Memorial Prize in Nervous Diseases*, B. Goodhead. *Priestley Smith Prize in Ophthalmology*, B. Goodhead and C. J. Roberts. *Douglas Marsh Ear, Nose, and Throat Prize*, G. R. Horton. *Leith-Newman Medical Prize in Pathology*, R. M. Finch. *Bostock Hill Memorial Prize in Social Medicine*, A. Rhodes. *Bertram Windle Prize in Anatomy*, A. Wakeling. *John Barritt Melson Memorial Prize in Physiology*, H. G. Percival. *Peter Thompson Prize in Anatomy*, Dorothy J. Bicknell.

[1]With second-class honours. [2]Distinction in paediatrics and child health. [3]Distinction in obstetrics and gynaecology. [4]Distinction in surgery. [5]Distinction in medicine. [6]Distinction in pharmacology and therapeutics. [7]Distinction in social medicine. [8]Distinction in forensic medicine and toxicology. *In absentia.

UNIVERSITY OF LIVERPOOL

The following candidates have been approved at the examinations indicated:

M.D.—B. J. Fairhurst, A. W. Howel-Evans, E. A. Nieman, J. R. Roberts, D. Taylor-Robinson, D. J. West.

PH.D.—*In the Faculty of Medicine:* K. Devakul.

CH.M.—E. C. Edwards, J. H. Y. Fung.

M.B., CH.B.—[1 2]R. Harris, [1 2]May B. Jones, H. M. Alty, A. L. Ansdell, W. K. H. Barnard, J. M. Beresford, G. N. Bhadresa, J. N. Boardman, Mary J. Boardman, M. J. Brindle, A. Broughton, T. N. Calvey, R. P. Christian, P. Cochrane, R. L. Coupe, Marie T. Cox, D. G. Ellis, E. R. Evans, R. E. Fallowfield, R. S. Ford, W. Green, Malvina Harris, J. Higham, L. J. Hipkin, Anne T. Irvine, J. A. Jackson, Anne Jacques, A. W. Jones, D. Jones, E. W. Jones, K. E. Jones, R. H. T. Jones, J. F. Kane, W. E. Kearns, N. B. Kirkland, K. Lilley, W. F. W. E. Logan, H. Martin, Maureen D. Martin, K. Martindale, P. J. Moorhead, Evelyn J. Moss, D. L. Parry, H. J. Phillips, G. H. Prince, P. G. Rae, G. B. Riley, Catherine O. L. Rimington, Aline M. Robertson, R. F. Robertson, C. Roby-Jones, J. M. Romer, Yvonne A. Roope, C. E. Sissons, J. F. Taylor, J. M. Taylor, R. W. Taylor, V. R. Taylor, N. E. Thomas, D. E. Wallace, R. Whitehead, J. G. M. Williams, J. A. Wilson, J. S. Wright, [3]W. D. R. Writer, C. Wynne. *Passed in separate subjects:* D. Cooper, R. F. Evans, and J. F. Farrall (surgery and obstetrics and gynaecology); D. D. Hughes (medicine and obstetrics and gynaecology); D. A. Hutchinson, G. W. Jones, and I. E. Roberts (medicine and surgery).

DIPLOMA IN PUBLIC HEALTH.—Sheila I. Angles, Cynthia J. Bladon, P. J. Burke, D. C. Curtin, A. Depares, Cecilia T. Diskin, F. R. Howell, J. V. Loughlin, Anne D. Micah, S. Naylor, J. M. V. Packer, J. A. Seddon, D. Wild.

DIPLOMA IN RADIOLOGY.—*Radiodiagnosis:* Varunee Amatyakul, E. H. Burrows, L. R. Levin, T. Nopparat, R. G. Pitman, H. G. Row. *Radiotherapy:* A. K. Bose, G. A. L. G. Blazebrook, R. Spencer.

[1]With second-class honours. [2]Distinction in surgery. [3]Distinction in obstetrics and gynaecology. [4]With distinction.

UNIVERSITY OF BRISTOL

Dr. T. J. Betteridge and Dr. L. A. Faigan have been appointed Demonstrators in Pathology.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in June was 116, compared with 87 in the previous month and 91 in June, 1957.

The numbers of cases of industrial diseases in the United Kingdom reported during June, 1958, were as follows: lead poisoning 2, aniline poisoning 1, compressed-air illness 1, anthrax 1, epitheliomatous ulceration 19, chrome ulceration 24; total 48. There were no deaths.—*Ministry of Labour Gazette*, July, 1958.

Week Ending July 26

The main feature of the return for England and Wales in the week ending July 26 was an increase in the notifications of food-poisoning by 154, from 332 to 486. Small fluctuations were recorded for other diseases. These included increases of 21 for scarlet fever, from 651 to 672, and of 6 for acute poliomyelitis, from 57 to 63. Falls in notifications were recorded for whooping-cough 78, from 827 to 749, measles 80, from 6,674 to 6,594, dysentery 75, from 712 to 637, and pneumonia 38, from 220 to 182.

The 63 notifications of poliomyelitis comprised 38 paralytic and 25 non-paralytic, which were respectively 1 more and 5 more than in the previous week. The largest return was from Yorkshire West Riding 16 (Leeds C.B. 5, Halifax C.B. 2, Normanton U.D. 2).

Two large outbreaks of food-poisoning were notified: Denbighshire, Abergele U.D. 139, and Lancashire, Formby U.D. 80.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing noti-

Is she suitable for oral diabetic treatment?

Many diabetic patients have now been stabilised on Rastinon tablets and inevitably other diabetics are wondering if they, too, can look forward to "treatment without injections." It has been estimated that about a quarter of all diabetics at present taking insulin in one clinic in Great Britain could be well controlled on Rastinon instead. (Lancet, 1957, **2**, 125)

SELECTION AND STABILISATION

The suitability of a patient can readily be determined in the diabetic clinic where selection and stabilisation are easily carried out. For those patients found to be suitable, Rastinon tablets provide a safe and effective form of therapy. No cases of proven dyshaemopoiesis or other serious side-effects due to the drug have been reported.

RASTINON
THE ORAL TREATMENT OF DIABETES

A SIMPLE AND ECONOMICAL TREATMENT

From 1 to 3 tablets a day are normally all that is required in suitable patients to replace the insulin. The usual regime of urine examination and dietary control remains necessary. The basic cost to the National Health Service of a week's treatment is on average between 3/6d. and 5/3d.

PACKS

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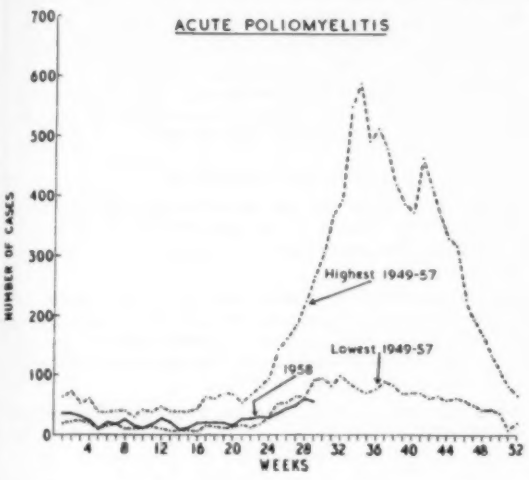
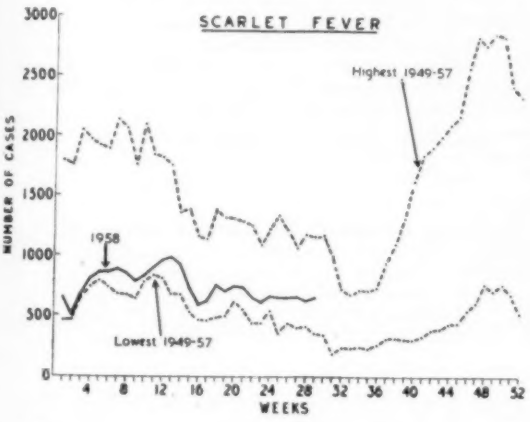
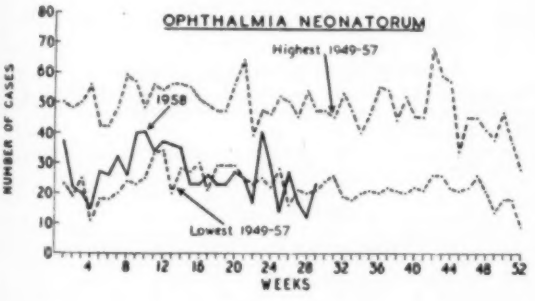
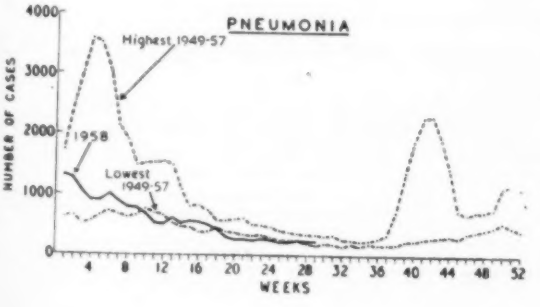
fications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 19** (No. 29) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	3	1	1	0		2	0	1	0	1
Dysentery ..	712	105	122	4	1	480	28	139	5	1
Encephalitis, acute	1	0		0		4	1		0	
Enteric fever:										
Typhoid ..	4	1	1	1		5	1	0	0	
Paratyphoid ..	4	0	2(B)	0	5(B)	5	0	0	1	
Food-poisoning ..	332	32	18	13		372	35	27	1	
Infective enteritis or diarrhoea under 2 years				13	18				7	32
Measles*	6,674	568	42	29	26	12,778	255	73	142	78
Meningococcal infection	15	0	12	0	1	16	1	6	2	
Ophthalmia neonatorum	23	2	6	0		21	2	2	0	
Pneumonia† ..	220	16	97	3	1	156	6	117	2	
Poliomyelitis, acute:										
Paralytic ..	37	3	21	3	7	105	7	3	14	5
Non-paralytic ..	20	1				84	10			
Puerperal fever§ ..	223	46	10	0		220	42	1	1	
Scarlet fever ..	651	37	31	8	14	544	37	59	16	23
Tuberculosis:										
Respiratory ..	578	62	71	22		596	63	97	20	
Non-respiratory	81	9	14	6		95	8	14	2	
Whooping-cough..	827	34	37	12	37	1,577	50	52	2	47

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	1	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	1	0		0			0	1	0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	2	0	1		0	7	0	2
Influenza	3	0	1	0	0		0	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	281	28	8	6	1		18	9	12	5
Poliomyelitis, acute	4	0		0	0		0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	49	5	5	1	2		5	4	0	3
Non-respiratory		3	2	0	0		0	0	0	0
Whooping-cough..	1	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	253	31	21	3	8		26	26	4	15
Deaths (excluding stillbirths) ..	7,842	632	464	102	126		652	512	104	125
LIVE BIRTHS..	13,732	1092	516	202	373		1151	983	231	384
STILLBIRTHS..	306	24	28				23	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Royal College of Physicians.—At the Quarterly Comitia held on July 31 with Dr. ROBERT PLATT, President, in the chair, the following officers were elected:

Censors: Drs. J. R. H. Towers, E. R. Cullinan, E. R. Boland, and J. C. Hawksley. *Treasurer:* Dr. R. R. Bomford. *Registrar:* Sir Harold Boldero. *Harveian Librarian:* Sir Charles Dodds. *Assistant Registrar:* Dr. J. R. Ellis. *Library Committee:* Drs. C. E. Newman, W. S. C. Copeman, W. Brockbank, and W. H. McMenemey. *Finance Committee:* Drs. L. C. Martin, J. F. Stokes, and J. W. D. Bull.

M.R.C.P.—The following, having satisfied the censors' board, have been admitted members of the Royal College of Physicians of London:

C. H. Ashton, G. V. Balmforth, J. L. T. Birley, D. F. Cappell, J. R. Curtis, C. T. Dollery, E. B. D. Dowdle, D. W. Evans, K. F. Fairley, O. W. Hill, W. B. Jackson, J. V. Jones, N. F. Jones, H. R. Klein, R. E. Lovelace, M. W. McNicol, V. Parsons, D. J. Patel, J. S. Penington, R. W. B. Penman, E. V. Pieris, A. Pollard, D. H. H. Pullon, A. M. Rankin, M. D. Readett, J. L. Reed, S. M. Richards, C. E. Rotem, H. H. Shawdon, C. K. Simpson, J. G. Sloman, M. A. Smith, A. E. Stevens, Squadron-Leader D. J. Stoker, M. W. Swallow, A. K. Thould, G. E. G. Williams, I. V. Wilson, J. Wilson, S. M. Woodcock, K. J. Zilkha.

Royal Medical Benevolent Fund.—At the annual general meeting held on July 30 the following honorary officials were re-elected: president, Sir HENRY TIDY; honorary treasurer, Mr. F. A. JULER; and honorary secretary, Dr. T. ANWYL-DAVIES. During 1957 the Royal Medical Benevolent Fund disbursed a total of £43,942 in grants and annuities. 97 of the 398 cases helped by grants were new. The annual report points out that the total number of people who benefit is much larger than the "cases," since many of these include married couples, children requiring financial help and education, and widows with families. Emphasizing the need for new subscribers, the report goes on: "Surprisingly enough, many of the profession do not know of its [the Fund's] existence or of its work. Many gladly subscribe when their attention is drawn to its purpose of acting as a Good Samaritan to the whole of the medical profession."

Royal College of Surgeons.—At a meeting of the council of the College on July 31 Lieutenant-Colonel R. H. ROBINSON, R.A.M.C., was awarded the Mitchiner Medal, and Wing Commander W. B. THORBURN was awarded the Lady Cade Medal. The award of the Gilbert Blane medal to Surgeon Commander W. E. CROCKER, R.N., was reported. The Handcock prize was awarded to Mrs. E. M. COOKE, of the Royal Free School of Medicine.

Medical Insurance Agency.—The thirtieth annual meeting of the Medical Insurance Agency was held in B.M.A. House on July 24. New records of business were achieved in all branches of the Agency's work last year, and new high levels of profits were allocated to the medical charities. Two new members were elected to the Committee of Management, Sir RUSSELL BRAIN and Sir CECIL WAKELEY. Retiring members re-elected were Dr. J. FENTON, Sir ARCHIBALD GRAY, Mr. A. M. A. MOORE, Mr. R. W. RAVEN, Dr. O. L. S. SCOTT, Mr. BEN THOMAS, and Sir HENRY TIDY. Dr. FENTON was re-elected chairman and Dr. HENRY ROBINSON as honorary secretary; a vote of thanks was passed to both of them for their services during the past year. The report of the committee contained an emphatic tribute to the work of the general manager, Mr. A. N. DIXON, and his staff.

Protein Extraction.—Among recent Rockefeller Foundation grants is one to help Dr. N. W. PIRIE, F.R.S., and his colleagues to help develop their machine for extracting edible protein from waste vegetable matter. The work is being carried out at the Rothamsted Experimental Station, Harpenden, Herts.

Biosynthesis of Protein.—The Royal Society has awarded a Mr. and Mrs. John Jaffé donation studentship from October 1 to Dr. Jennifer Wildy to work on the biosynthesis of the protein and haem components of haemoglobin in the department of chemical pathology, University College Hospital Medical School.

Dr. W. J. H. Butterfield has been appointed to the university chair of experimental medicine tenable at Guy's Hospital Medical School.

Surgeon Captain C. B. Nicholson has been appointed an honorary surgeon to the Queen in succession to Surgeon Rear-Admiral E. T. S. RUDD.

COMING EVENTS

British Association for the Advancement of Science.—Annual meeting, August 27 to September 3, in Glasgow. Details from the association, 18, Adam Street, Adelphi, London, W.C.2.

Institute of Biology.—Symposium on "The Effects of Pollution on Living Material," September 25 and 26, at the Royal Geographical Society, London, S.W.7. Further details from the general secretary of the Institute of Biology, 41, Queen's Gate, London, S.W.7.

Sixth International Congresses on Tropical Medicine and Malaria.—To be held in Lisbon from September 5 to 13. Further information from Professor Dr. MANUEL R. PINTO, Instituto de Medicina Tropical, Lisbon, Portugal.

International Association of Gerontology.—First meeting of the European Clinical Section, October 1–4 in Sunderland. Details from Dr. E. WOODFORD-WILLIAMS, Department of Geriatrics and Medicine, the General Hospital Chester Road, Sunderland, Co. Durham.

South African Paediatric Association.—Fourth congress, October 9–11, at the Pretoria Hospital. Further details from the secretary, Dr. E. FASSER, 201, Medical Centre, Pretoria, South Africa.

Conference on General Practice.—The *Medical World* is holding a conference on October 26 at the Victoria Halls, Bloomsbury Square, on general practice topics such as emergencies, rehabilitation, and the doctor–patient relationship. Admission by ticket (10s. 6d.). Further details from the *Medical World*, 55–56, Russell Square, London, W.C.1.

NEW ISSUES

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Friday, August 15

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: clinical demonstration.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—K. M. Mackenzie, M.D., M.R.C.P., Part-time Consultant Physician, West Suffolk General Hospital; J. H. Roberts, M.B., Ch.B., Radiological Registrar, Ipswich and East Suffolk Hospital; J. H. A. Black, M.B., B.Ch., and D. F. Craggs, M.B., B.S., Registrars in Psychiatry, Fulbourn and Addenbrooke's Hospitals; H. L. Clarke, M.B., B.S., Anaesthetic Registrar, Newmarket General Hospital.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Ostlere.—On July 29, 1958, at King's College Hospital, London, S.E., to Mary (formerly Patten), M.B., Ch.B., M.R.C.P.Ed., F.F.A. R.C.S., and Gordon Ostlere, M.B., B.Chir., F.F.A. R.C.S., of 22, St. George's Road, Bickley, Kent, a daughter—Katharine Mary.

Shemilt.—On July 25, 1958, at Salisbury Infirmary, Wilts, to Janet (formerly Brownscombe), wife of Mr. Philip Shemilt, a daughter.

DEATHS

Smith.—On July 24, 1958, at his home, Ascot, Berks, Malcolm Arthur Smith, M.R.C.S., L.R.C.P., aged 82.

Upton.—On July 22, 1958, in hospital, Bryan Harold Burgin Upton, M.B., Ch.B., of "Brentwood," Long Street, Dordon, Tamworth, Staffs.

Worthington.—On July 23, 1958, at the home of his son, Stanley Worthington, M.D., D.P.H., B.Hy., of the Grange, Leeds.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Prednisolone and Pregnancy

Q.—*Is pregnancy in a young woman being treated with prednisolone, 5 mg. daily, for severe eczema an indication for stopping treatment?*

A.—This dose of prednisolone is very unlikely to have any effect on pregnancy or on the foetus. However, in experimental animals developmental anomalies appear to have been produced when steroids are given during pregnancy. Although this is not known to occur in man it perhaps sounds a note of caution. It seems very unlikely that any other complications will ensue on the dosage mentioned. At the same time it is questionable whether 5 mg. of prednisolone daily would have very much effect on the eczema. Eczema is subject to spontaneous remissions and relapses, and it may well be that the patient mentioned is now in a partial remission and that the prednisolone is not really having much effect. In the circumstances, therefore, the prednisolone might be stopped and resumed at the same dosage only if it is quite clear that the patient's condition has materially deteriorated as a consequence. The effect of pregnancy on eczema is variable and usually unpredictable. Some patients improve, some get worse, and the majority are not affected.

Sequestrene

Q.—*Is sequestrene as good in laboratory work as Wintrobe's double oxalate? May sequestrenized blood be used for all those investigations for which blood anticoagulated by Wintrobe's method may be used?*

A.—Sequestrene (E.D.T.A.) is at least as good in laboratory work as Wintrobe's double oxalate and for certain purposes rather better. Blood in sequestrene can be used for all those investigations for which Wintrobe's oxalate mixture is normally used.

The main advantage of sequestrene is its ability to preserve the cellular elements of the blood for a longer period than is possible with the double oxalate mixture.[1] If the correct amount of sequestrene is used, there are no obvious morphological changes in the white cells up to 4–5 hours after collection of the blood. Total red and white cell counts may be carried out up to 24 hours after collection of the blood. Sequestrene is a particularly good anticoagulant for platelets not causing any appreciable clumping or disintegration, allowing platelet counts to be made up to 6–8 hours after collection of the blood. As it is non-toxic, sequestrene is also a suitable anticoagulant for fresh blood transfusions of platelets.

Two salts of ethylene-diamine tetra-acetic acid have been used as anticoagulants—the disodium salt has been more widely used, but the dipotassium salt is probably better owing to its greater solubility (seven times as great in water.)[2] Both salts of E.D.T.A. may be used in a similar way. For routine haematological procedures the salts are best used in the dry form. A 10% solution in distilled water is prepared. 0.1 ml. is placed in tubes or bottles marked at 5 ml. The solution is allowed to dry at room temperature, giving 5 mg. of E.D.T.A. in each bottle, which is sufficient for 5 ml. of blood. The bottles should not be placed in a hot-air oven to dry, as this tends to make E.D.T.A. relatively insoluble. The other way to use sequestrene is as a 3% solution in 0.7% sodium chloride solution, when 0.5 ml. is sufficient to stop 9.5 ml. of blood from clotting.

REFERENCES

1 Hadley, G. G., and Larson, N. L., *Amer. J. clin. Path.*, 1953, **23**, 613.
2 —— and Weiss, S. P., *ibid.*, 1955, **25**, 1090.

Hypertrophy of Prostate

Q.—*What is the present view on the aetiology of the hypertrophy of the prostate, and what are the earliest and average ages of its manifestation?*

A.—The consensus of opinion is that hypertrophy of the prostate is due to hormone imbalance, but much experimental work and many therapeutic trials have given inconclusive results as to the exact mechanism.[1] Other theories that it is due to neoplasia, arteriosclerosis, or inflammation contain too much conflicting evidence to be tenable. Both histological and clinical evidence shows that the changes in the gland begin at about the age of 40 and are maximum at about 60. Within the past year two patients aged 42 have been seen with retention due to prostatic hypertrophy, but this is most uncommon and the clinical manifestations of the condition are most frequent from the age of 60. The changes may continue or the condition may remain stationary. Schinz and Reich[2 3] have shown from mortality statistics that there is a true age predisposition to the disease. Franks[4] found from necropsy material that 80% of men over 80 years old had prostatic enlargement. The need for surgical as opposed to conservative treatment depends on the obstructive changes produced in the kidneys and on the amount of inconvenience or loss of sleep caused by nocturnal micturition.

REFERENCES

1 Thomson, R. V., and Ash, J. E., in *Urology*, 1954, edited by M. Campbell, vol. 2, chap. 4. Saunders, Philadelphia and London.
2 Schinz, H. R., and Reich, Th., *Dtsch. med. Wschr.*, 1956, **81**, 439.
3 —— —— ibid., 1956, **81**, 572.
4 Franks, L. M., *Ann. roy. Coll. Surg. Engl.*, 1954, **14**, 92.

Cruikshank's Hypothesis

Q.—*Apart from statistical evidence, has any bacteriological, virological, or animal experimental evidence been found or sought in favour or confutation of Cruikshank's hypothesis?*[1]

A.—Cruikshank's statistical studies suggested to him that, as the mortality from pulmonary tuberculosis falls and the number of individuals with arrested tuberculosis rises, the mortality rate from lung cancer will also rise. To account for this he enunciated the purely speculative hypothesis that the body of the tubercle bacillus contains a series of carcinogenic phages and that destruction of bacilli in the lung will liberate these carcinogens, which eventually induce lung cancer. The tubercle bacillus has been exhaustively investigated and no claim has been made that it contains a bacteriophage, but there are no reports that an exhaustive but unsuccessful search for a specific bacteriophage has been made.

REFERENCE

1 Cruikshank, D. B., *Papworth Research Bulletin*, 1939, No. 2, p. 1. Pendragon Press, Papworth.

Operation Stockings

Q.—*Are those long woollen stockings, known as operation stockings, now considered necessary?*

A.—Although long woollen stockings are still widely used there is no doubt that they are quite unnecessary at the time of operation. Fashion and tradition die hard in medicine, and this is particularly true of some routine nursing procedures. The ritual use of purges and enemas took many years to expunge, and even to-day these practices are kept alive in some hospitals. The abolition of operation stockings may take as long.

The long stocking was mainly introduced as an anti-shock measure in the era when we thought it right to keep patients as warm as possible. Our views on shock have changed a good deal in the last decade or two, and it should now be recognized that these stockings are not only unnecessary but frequently positively objectionable. They are unnecessary because a patient confined to bed in a warm hospital ward, or transferred to a properly prepared

theatre trolley, should certainly not suffer from cold feet. They are objectionable because they commonly carry pathogenic organisms from the ward into the operating theatre. Ordinary laundering of woollen stockings tends to spread pathogenic organisms between the various articles and does not sterilize them. If stockings are autoclaved or boiled they will, of course, shrink badly. If surgeons insist on using such stockings, then they should equally insist on having them sterilized, and this can be done in formalin vapour without damage to the wool. Alternatively, stockings can be made of other materials which are resistant to autoclaving.

Salt and Hypertension in the Tropics

Q.—*Should an elderly man with some hypertension (170/110) of ten years' duration, proceeding to the tropics, take added salt in his diet to prevent heat exhaustion? He has been on a salt-reduced diet for years.*

A.—In this patient the hypertension is not severe, perhaps as a result of the low-salt diet he has been taking. It would be helpful to know whether there are any hypertensive complications such as heart failure, renal insufficiency, or cerebral vascular disease. The use of salt additional to a normal diet cannot be advised, as it might precipitate heart failure and would certainly increase the blood pressure. The patient should continue with moderate salt restriction and do his best to avoid situations where excessive sweating is likely to occur over long periods, which should not be too difficult with modern facilities for cooling houses and places of work in the tropics. If appreciable chronic renal insufficiency is present, residence in the tropics is inadvisable.

Cross-Channel Swimming

Q.—*What emergencies should a doctor be ready for when accompanying a cross-Channel swimmer?*

A.—Medical emergencies during the organized cross-Channel swims have been notably absent. The obvious risk is that of drowning. This may be precipitated by exhaustion and chilling, inhalation of vomitus during seasickness (from which the swimmers do suffer), helplessness due to cramps, drowsiness due to premedication with sedative drugs, injury due to being struck by some object (including the accompanying boat), and possible separation from the boat. Artificial respiration should be given at the earliest opportunity and time should not be wasted in clinical examination of any description. The Holger Nielsen method is not only one of the most efficient, but it is the method most practicable in the cramped conditions usually present in an accompanying boat, which may possibly be pitching and rolling. Success depends on the absence of delay in starting aeration. Pure oxygen is desirable, but its administration should be left to someone other than the doctor until normal respiration has been restored. Delay in starting artificial respiration may be caused by difficulty in getting the unconscious grease-covered swimmer into the boat, but a roller towel placed under the axillae will facilitate this operation.

It should be mentioned that, although spontaneous respiration may be restored within a few minutes, the victim may remain unconscious for some hours. A careful watch should be kept on the breathing during this unconscious phase, as respiration may fail again as a result of the hypoxia due to the gross pulmonary oedema which accompanies near-drowning.

Chilling may be sufficiently severe to cause retirement. The swimmer should be dressed as quickly as possible in woollen clothing and an outer windproof garment. Exercise and an ample supply of a hot drink—tea or coffee—are the therapeutic procedures. Degreasing should be left until later. Cramp may be severe and painful. Warmth and physiological rest are necessary; morphine is rarely likely to be required. Retention of urine and distension of the bladder may occur in those who float on their backs for long periods in cold water. This has been observed experimentally in association with the greatly increased urine output in these circumstances, but it has not been reported in Channel swimmers.

The equipment bag should contain the obvious dressings for minor surgical treatments. Salt-water conjunctivitis can scarcely be described as an emergency, but it does occur, and room might be found for a dropper and a bland lotion or liquid paraffin. If it is intended to provide any anti-seasickness remedy it would be advisable to make sure beforehand that the competitor has no idiosyncrasy to whatever preparation is used. Except for a roller towel, no special items which common sense does not suggest need be carried in the emergency bag. But the value of the towel cannot be overstressed.

NOTES AND COMMENTS

Steroid Therapy and Resistance to Infection.—Professor D. A. LONG (Pittsburg, Pennsylvania, U.S.A.) writes: In reply to the question, "Is resistance to colds and other infections reduced during corticosteroid therapy?" ("Any Questions?" May 17, p. 1191), your expert states, quite correctly, that in experimental animals steroids may convert a trivial infection into a malignant one, but that in practice the risk of doing so in man is slight. Indeed, the dose of steroid should be increased during infection. He implies that the reason for this rather paradoxical state of affairs is that there is no relationship in terms of dose per kg. between the therapeutic dose in man and that required to cause septicaemia and death in animals. This is not true. The explanation for this difference is important, and indeed vital, to an understanding of research in this field and to future research on this subject. Rats, mice, and rabbits infected with bacteria and treated with corticosteroids develop overwhelming infections and die, Rhesus monkeys and guinea-pigs do not. These species may be termed "cortisone-sensitive" and "cortisone-resistant."[1] Man belongs to the latter group and shares with them several important interrelated analogous features. The evidence for these statements has been reviewed in a recent paper.[1]

REFERENCE

1 Long, D. A., *Int. Arch. Allergy*, 1957, **10**, 5.

Halitosis.—Dr. L. MCGOLRICK (Dublin) writes: Your expert's reply ("Any Questions?" July 12, p. 117), in common with many other annotations I have seen on this subject in the past, has failed to point out what I consider to be the most common cause of this embarrassing complaint in subjects whose dentition is perfect and who have neither naso-oral sepsis nor pulmonary nor gastro-intestinal disease. That is the presence of minute fragments of putrefying protein material persisting between the molars, usually the upper. These resist removal in many cases even by the most meticulous brushing, and the only remedy is the routine use of dental floss, "stimudents," or the non-U toothpick. An occasional exploration with the latter and the presentation of the result to the olfactory organ will offer a surprise and explanation to those who find their best friends averting their faces on occasions.

Collected Articles from the "British Medical Journal"

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